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# SURGERY

*A Monthly Journal Devoted to the Art and Science of Surgery*

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# SURGERY

VOL. 27 FEBRUARY, 1950 No. 2


## Original Communications

### POSTPHLEBITIC SYNDROME

#### TREATMENT BY CONSERVATIVE MEASURES, SYMPATHECTOMY, AND OTHER OPERATIVE MEASURES


ALTON OCHSNER, M.D., MICHAEL DEBAKEY, M.D.,* PAUL T. DECAMP, M.D., IRVING M. RICHMAN, M.D., CHARLES J. RAY, M.D., RAEBURN C. LLEWELLYN, M.D., AND OSCAR CREECH, M.D., NEW ORLEANS, LA.

*(From the Department of Surgery, School of Medicine, Tulane University of Louisiana, Charity Hospital of Louisiana, and the Ochsner Clinic)*


#### INTRODUCTION

BECAUSE of the recent increased interest in venous thrombosis much has been learned regarding its etiology, prevention, and treatment. Unfortunately, either because of lack of adequate therapy or because of failure of the patient to respond to the prescribed treatment, a disabling complication, the postphlebitic syndrome, develops in many of these patients. Jorpes[1] stated that in Sweden the postphlebitic syndrome caused more disability than sequelae following automobile accidents. Zilliacus[2] reported that of 680 patients who had had phlebitis from six to fourteen years previously, 90 per cent had persistent discomfort and 20 per cent had ulcers. It was a study of our experience with these unfortunate individuals that prompted this report.

As has been emphasized in previous publications,[3-10] most postphlebitic complications are preventable, and unquestionably in the future fewer persistent sequelae will develop because of the presently employed prompt and adequate therapy during the acute phase of thrombophlebitis. Whereas much has been written concerning venous thrombosis, little attention has been paid to the persistent and disabling sequelae, which, with the exception of phlebothrombosis and pulmonary embolism, in reality are much more serious than the originating thrombosis. It is true that the patient with phlegmasia alba dolens is temporarily incapacitated because of the acute thrombophlebitis, but the persistence of symptoms in the inadequately treated or untreated patient produces disability for years and frequently for the rest of the patient's life.

We[9, 11] previously demonstrated both clinically and experimentally that the symptoms in acute thrombophlebitis are due largely to spasm of the homo-


Annual E. Starr Judd Lecture delivered at the University of Minnesota, Minneapolis, Minn., Jan. 18, 1949.

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lateral arterioles resulting from impulses originating in the thrombophlebitic segment which are carried over the sympathetic nervous system to the arterial system. Vasodilatation produced at this stage of the process results in prompt resolution and subsidence of symptoms. Because of the splendid results obtained by interruption of the vasoconstrictor impulses in the acute phase of thrombophlebitis, an evaluation of vasodilatation in the treatment of persistent postphlebitic sequelae seemed justified. Variable results obtained by sympathectomy in the treatment of the postphlebitic syndrome have been recorded. Goinard[12] reported a successful result in a patient with postphlebitic sequelae in whom other methods of treatment had failed. Homans[13] believed that certain postphlebitic sequelae, consisting of pain which develops early in convalescence associated with vasomotor changes in the skin, are benefited by sympathectomy. Similarly, beneficial results have been reported by Adams,[14] Gravelle and O'Donnell,[15] McPheeters and Alexander,[16] and Borrie and Barling.[17] On the other hand, Linton and Hardy,[18, 19] Gordon,[20] and de Takats[21] have not obtained satisfactory results from this method of treatment of the postphlebitic syndrome.

Our interest in the possible role played by arteriolar spasm in persistent postphlebitic edema was stimulated slightly over a decade ago by beneficial results obtained by procaine block of the regional sympathetic ganglia in a patient with persistent, disabling edema resulting from severe thrombophlebitis six years previously. In order to determine which patients might be benefited by vasodilatation a relatively simple test was devised. Careful circumferential measurements of the involved extremity are made at several levels. Using a bony line mark such as the knee joint space as one measurement, the examiner chooses two levels on the leg, one at a prominent portion of the calf and one just above the ankle, and two on the thigh. After the circumference of the extremity has been determined at each of the five levels, the patient is instructed to walk at his normal gait for a distance of approximately one mile, after which measurements are again made and procaine block of the regional sympathetic ganglion is performed. The patient then again walks the same distance at the same rate of speed, following which measurements of the extremity are remade and compared with the two previous measurements. If the circumference of the extremity has decreased following sympathetic block, we have felt justified in assuming that vasospasm is probably a factor in producing the edema.

In patients in whom improvement followed procaine anesthetization of the regional sympathetic ganglia, efforts were made to secure vasodilatation. Measures employed consisted of avoidance of vasoconstrictor influences, such as smoking, exposure to cold, and emotional upsets. In addition, the patients were instructed to apply compression bandages (ACE No. 8, lastex) before arising in the morning. Occasionally elastic stockings were allowed. We prefer bandages, however, because although an elastic stocking is easier to apply and slightly less objectionable to the patient, it has the disadvantage of not fitting properly after a few days because of stretching. Even though an elastic bandage stretches, it may be applied daily to conform to the size of the leg on

that particular day. In many patients, especially those with mild postphlebitic manifestations, conservative therapy will sufficiently ameliorate symptoms to permit the patient to pursue a useful life. With few exceptions in our cases conservative measures were instituted initially and we resorted to radical measures only after conservative therapy failed to relieve the disabling manifestations.

In less than one-half of our patients in whom vasospasm apparently was responsible for persistence of symptoms, sympathectomy was advised. Generally, this was reserved for the more severe cases and for patients in whom disability was more significant; that is, a man is more severely handicapped by postphlebitic sequelae than a housewife who, although disabled, can arrange her duties in such a way as to obtain optimum periods of rest during the day.

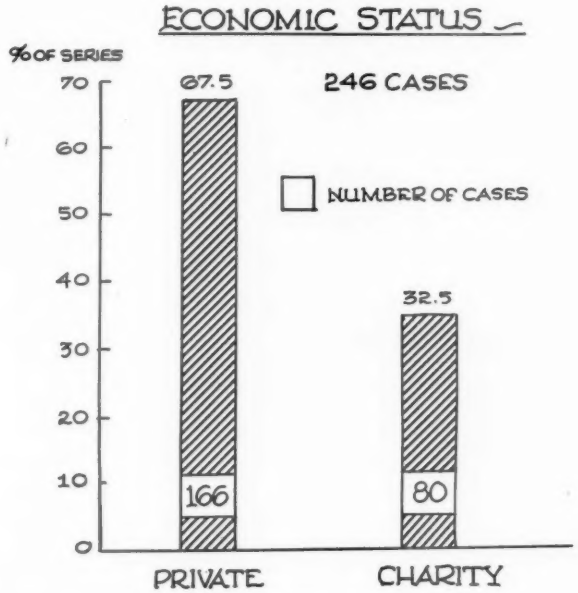



Fig. 1.

ANALYSIS OF CASES

During the six-year period ending October, 1948, we have treated approximately 600 patients with the postphlebitic syndrome, 246 of whom have been adequately followed for a period of six months or longer; this group forms the basis of this study. Patients seen within the past six months are not included. Although the entire group of cases was not analyzed, this is an unselected pilot study with careful follow-ups and evaluation of the cases. Of the 246 cases, 166 (67.5 per cent) were private patients treated at the Ochsner Clinic and 80 (32.5 per cent) were seen in the outpatient department or wards at Charity Hospital in New Orleans (Fig. 1).

*Etiology.*—The cause of the original thrombophlebitis in this series varied considerably. Of the 246 cases, 76 (30.9 per cent) occurred postoperatively; 40 (16.3 per cent) post partum; 39 (15.9 per cent) followed a severe infection, such as typhoid fever or pneumonia; 30 (12.2 per cent) occurred spon-

taneously; 29 (11.8 per cent) were of unknown etiology; 23 (9.3 per cent) were posttraumatic; and 9 (3.7 per cent) began as a thrombophlebitic process in varicose veins (Fig. 2). Undoubtedly in many of this last group, the cause was spontaneous, although it was not so stated in the record. It is of interest that in 12 per cent of the cases no cause for the venous thrombosis could be found. These figures differ somewhat from those of Linton and Hardy,[19] who noted that in 49 cases thrombosis occurred postoperatively in 40.8 per cent and postpartum in 32 per cent, was associated with medical diseases in 16 per cent, and was spontaneous in only 4 per cent.

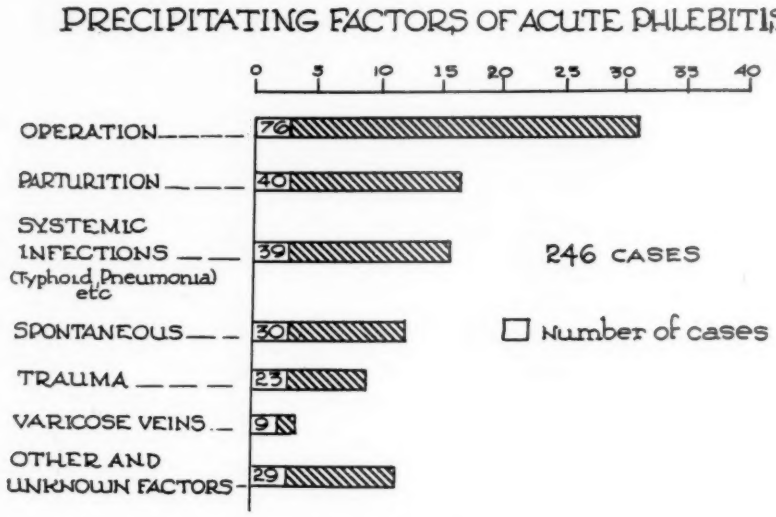



Fig. 2.

*Incidence.*—Of 242 cases in which the age was stated, the greatest number occurred in the third, fourth, and fifth decades (26 per cent, 26.5 per cent, and 21.1 per cent, respectively) (Fig. 3). Only 10 per cent of patients were in the first two decades of life, and 16 per cent were over 50 years of age.

Postphlebitic sequelae occur slightly more frequently in women than in men, probably because phlebitis develops more often in the former. Of our 246 patients, 140 (56.9 per cent) were females and 106 (43.1 per cent) were males (Fig. 4). In Linton and Hardy's[19] series 63 per cent were females and 37 per cent males.

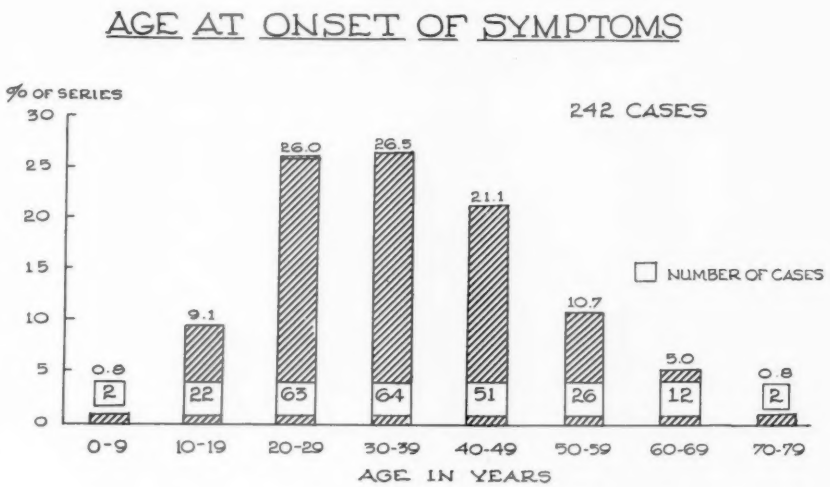
As is well known, thrombophlebitis occurs more frequently in the left lower extremity than in the right, undoubtedly because of the greater amount of vascular stasis on the left side. As might be expected, the incidence of postphlebitic sequelae in our series was higher on the left (51.7 per cent) than on the right side (24.4 per cent). The involvement was bilateral in 23.9 per cent (Fig. 5).

*Classification of Cases.*—In order to analyze the results of therapy satisfactorily, it was considered desirable to classify the cases according to the severity of the disease. The cases were thus divided into four groups:

1. Asymptomatic—patients with no symptoms or signs of disease and no disability. This was observed only following therapy.

2. Mild disease—patients with mild to moderate edema, no significant complications, slight or no pain, and slight or no disability. This group included all patients who obtained complete relief of symptoms by the use of compression bandages.

Fig. 3.



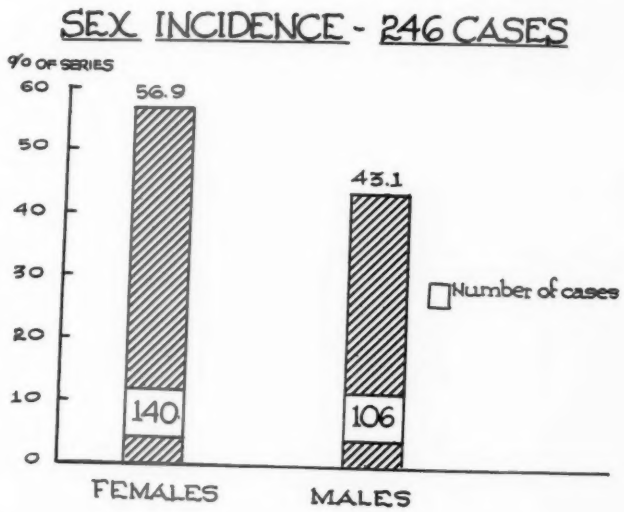



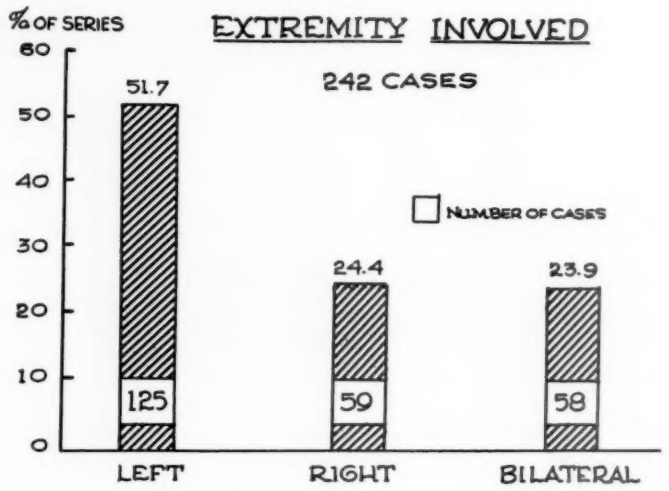

Fig. 4.

3. Moderately severe disease—patients with moderate edema, no recent history of complications, mild to moderate pain, disability limiting essential activities.
4. Severe disease—patients with severe edema, moderate or severe pain, presence, or recent history, of complications, disability limiting essential activities.

*Clinical Manifestations.*—Edema was present in all patients. Other disabling manifestations were pain, which occurred in 63.8 per cent, ulcers in

31.3 per cent, recurrent phlebitis in 24 per cent, and recurrent cellulitis or erysipeloid infection in 23.6 per cent (Fig. 6). Linton and Hardy[19] observed edema in 100 per cent of their patients, pigmentation in 95 per cent, varicose veins in 94 per cent, pain in 64 per cent, stasis dermatitis in 59 per cent, stasis cellulitis in 57 per cent, and ulceration in 43 per cent.

Fig. 5.



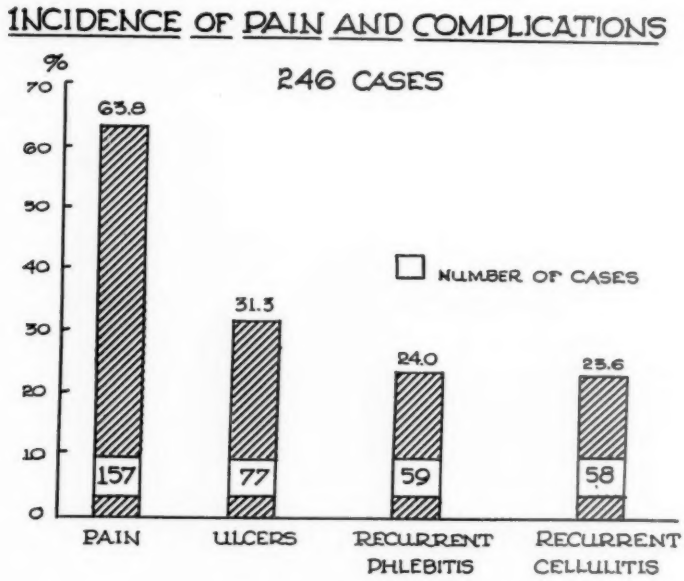
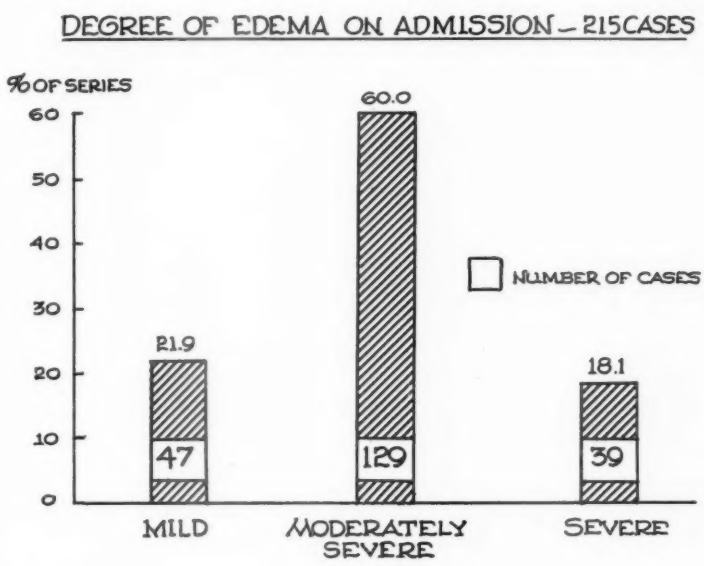




Fig. 6.

Edema was a prominent manifestation in practically all cases, and in 215 of the cases in which the description was adequate to justify its classification according to the degree of severity, 21.9 per cent were classified as mild, 60 per cent as moderately severe, and 18.1 per cent as severe (Fig. 7).

The more severe manifestations were observed in men, possibly because women are more cognizant of milder symptoms, such as slight edema, and seek medical assistance when a man will not. Of the 106 men, 14.2 per cent had mild symptoms, 48.1 per cent had moderately severe and 37.7 per cent had severe manifestations. These respective percentages in the 140 women were 22.9 per cent, 50.7 per cent, and 26.4 per cent (Fig. 8). Approximately 70 per cent of the mild cases were in women and 30 per cent were in men. Of

Fig. 7.



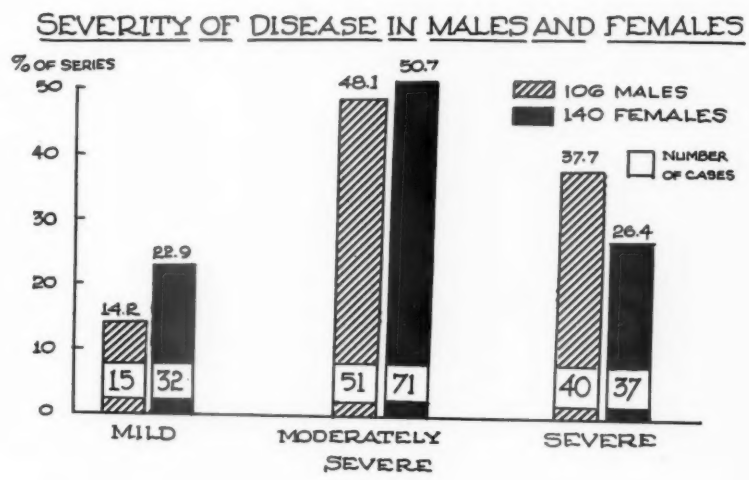



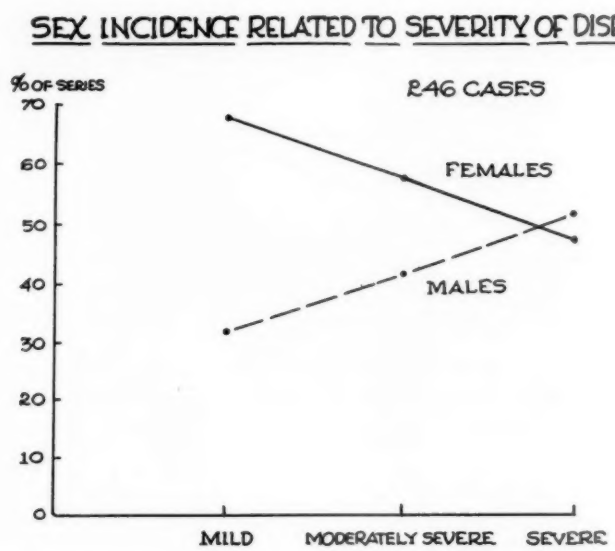

Fig. 8.

the moderately severe, the respective percentages were approximately 60 and 40, whereas in the severe cases more men were involved than women, the percentages being 55 and 45, respectively (Fig. 9).

*Duration of Disease.*—Of 244 patients in whom the duration of the disease (time elapsing since original phlebitis) prior to admission was definitely stated,

43 (17.6 per cent) had had symptoms less than six months; 49 (20.1 per cent) had symptoms from six months to two years; 44 (18 per cent) from two to five years; 43 (17.7 per cent) from six to nine years; and the largest group, 65 cases (26.6 per cent) ten years or longer (Fig. 10). In Linton and Hardy's[19] group of 32 patients with ulceration only 12.5 per cent had symptoms less than one year; 40 per cent for five years; 22 per cent for six to ten years, and 38 per cent over ten years.

Fig. 9.



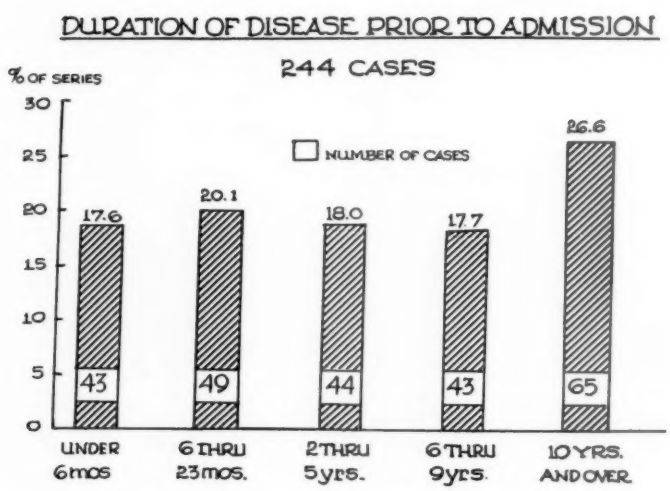
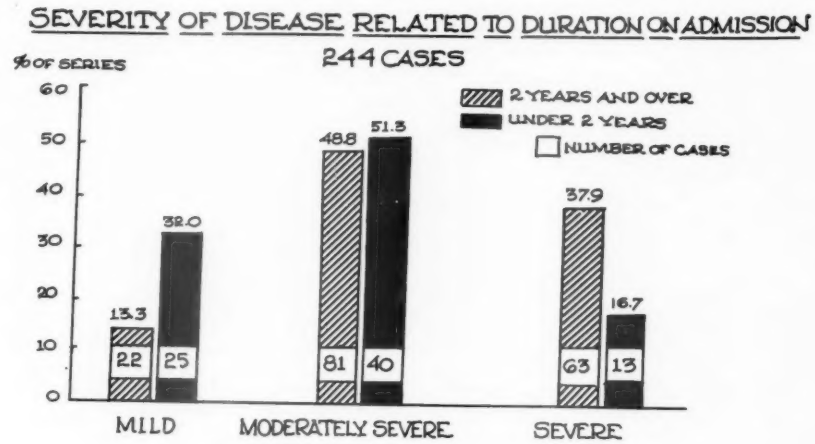




Fig. 10.

If one considers the severity of the disease according to the length of time elapsed since the originating phlebitis, interesting results are obtained. Generally milder symptoms were seen in patients with shorter periods of involvement. An arbitrary dividing line of two years was chosen. In patients who had had the complication on admission less than two years 32 per cent

had mild, 51.3 per cent had moderately severe, and only 16.7 per cent had severe disease. Of patients who had had the syndrome on admission more than two years, only 13.3 per cent had mild disease, 48.8 per cent had moderately severe, and 37.9 per cent had severe disease (Fig. 11). Stated in a slightly different way, of the patients whose disease was classified as mild on admission, 53 per cent had been ill less than two years; in the moderately severe group 33 per cent had had symptoms for less than two years, whereas

Fig. 11.



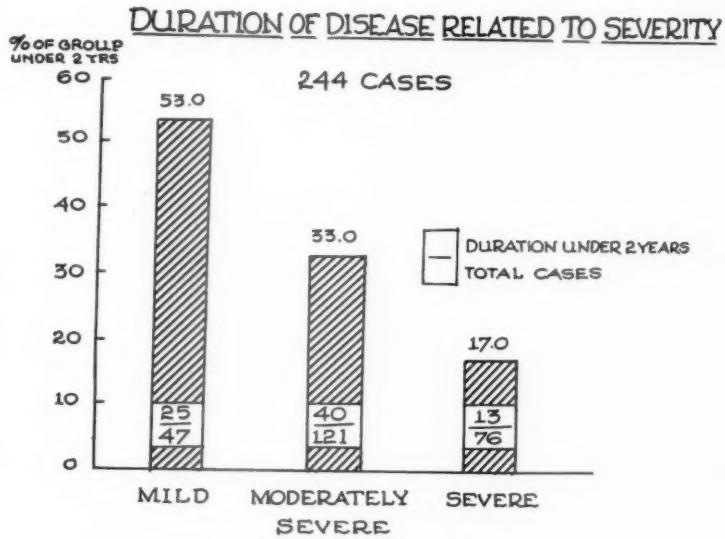
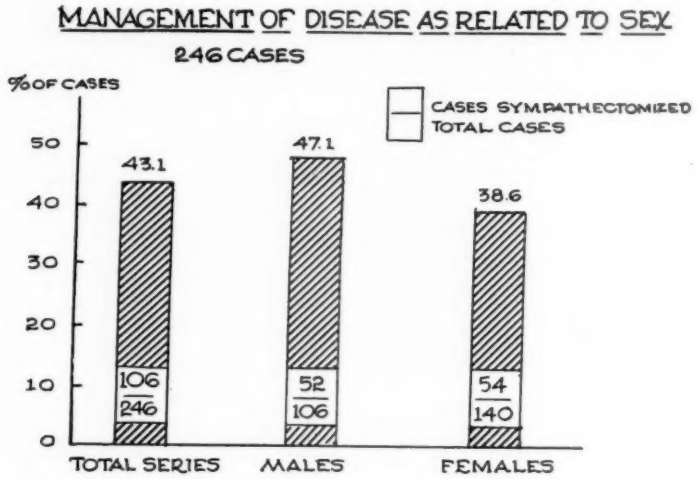




Fig. 12.

in the severe group only 17 per cent had had the disease less than two years (Fig. 12). In other words, the longer the interval between the originating phlebitis and admission, the more likely are the symptoms to be severe. This may be due to one or more of several factors: the milder cases may tend to regress with time, the severe cases may tend to become worse, or patients may seek consultation only after considerable time has elapsed.

*Type of Treatment.*—As mentioned previously, the treatment of postphlebitic sequelae consists of conservative measures to prevent vasoconstriction and to produce vasodilatation. In the present series 57 per cent of the patients were treated by conservative measures, whereas 43 per cent had sympathectomies. In 53 patients (21.5 per cent) other radical procedures were also employed. Generally, because disability in a man who is usually

Fig. 13.



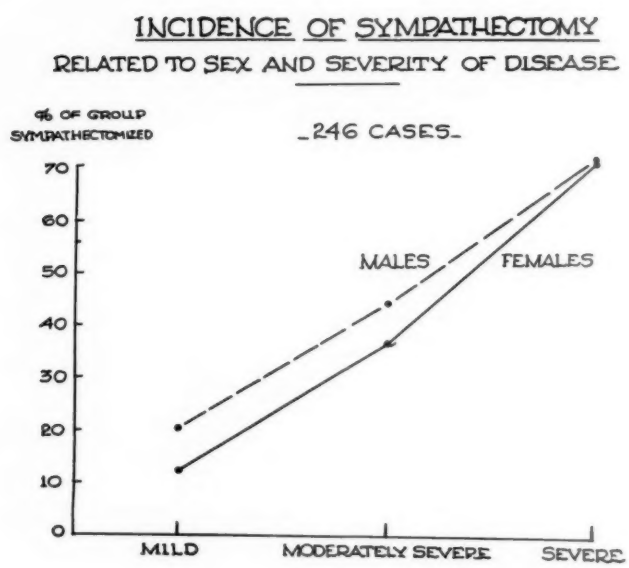



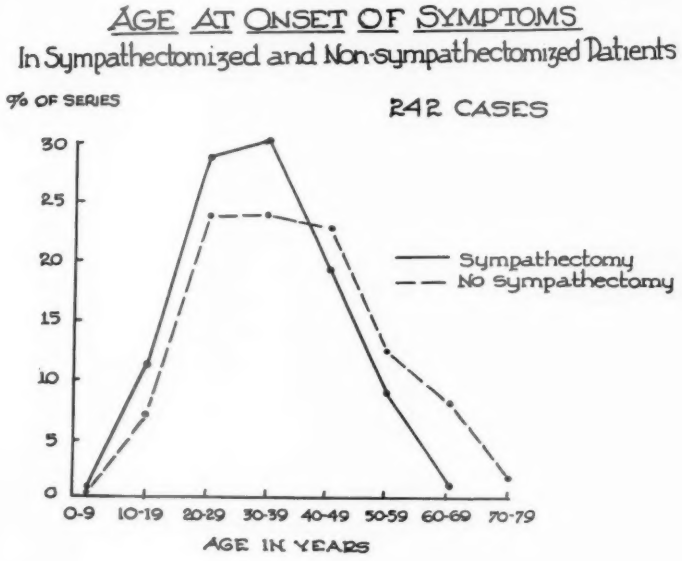

Fig. 14.

a wage earner is more significant than a similar disability in a woman, sympathectomy was done more frequently in men (47.1 per cent) than in women (38.6 per cent) (Fig. 13). This was true in the mild and moderately severe group, but in the severe cases sympathectomy was employed with equal frequency in both sexes (Fig. 14). Thus, in women with milder symptoms con-

servative measures were generally sufficient to relieve symptoms. Sympathectomy was also used in a higher percentage of younger people and was rarely performed in patients more than 50 years old (Fig. 15).

Radical measures were rarely employed in the treatment of the mild (14.6 per cent) and moderately severe (38.8 per cent) manifestations, but fre-

Fig. 15.



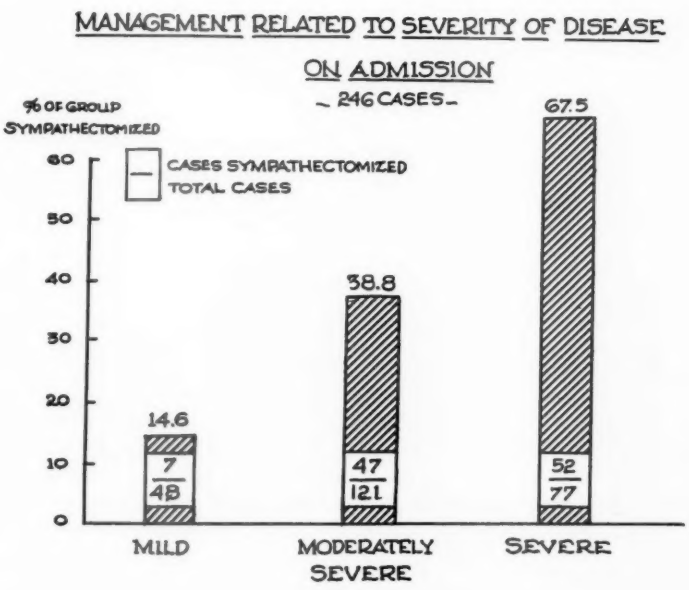
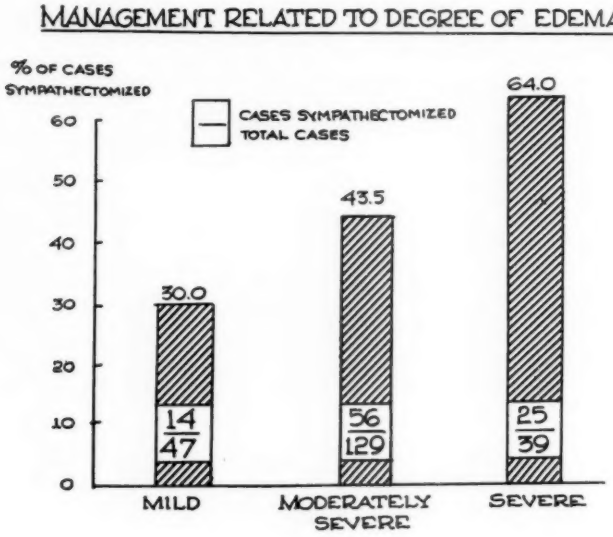




Fig. 16.

quently were considered necessary in severe cases (67.5 per cent) (Fig. 16). Of the 215 cases in which edema was adequately described to permit classification, sympathectomy was employed in 30 per cent of the mild, in 43.5 per cent of the moderately severe, and in 64 per cent of the severe cases (Fig. 17).

Of the 140 patients treated conservatively, 28.6 per cent had mild disease, 53.5 had moderately severe, and only 17.9 per cent had severe disease. On the other hand, of the 106 treated by sympathectomy 6.6 per cent had mild manifestations, 44.3 per cent had moderately severe, and 49.1 per cent had

Fig. 17.



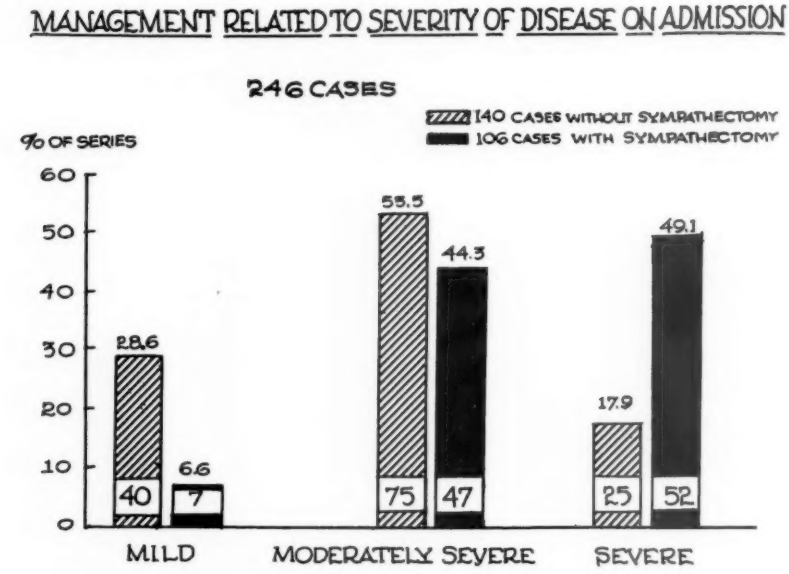




Fig. 18.

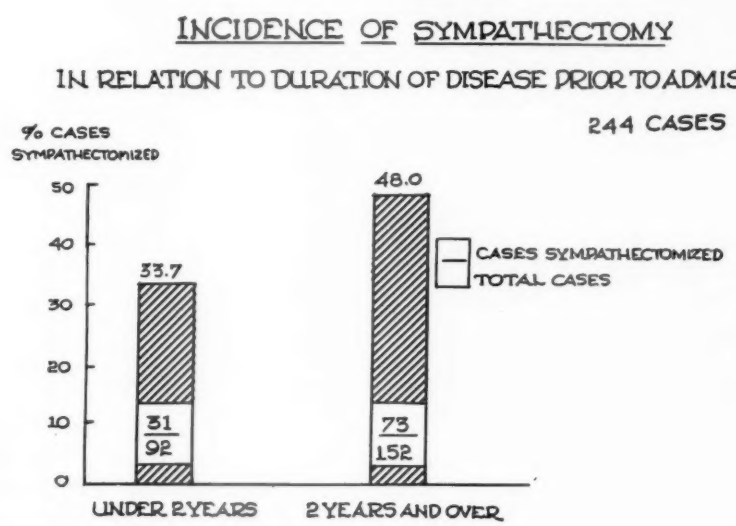
severe symptoms (Fig. 18). Although the group of patients with mild symptoms treated by sympathectomy is too small to justify valid conclusions, the excellent results obtained suggest that sympathectomy probably should be used more often in the mild and moderately severe cases.

Of the 92 patients who were seen within two years of the original attack of phlebitis, 31 (33.7 per cent) were subjected to sympathectomy, whereas of

the 152 in whom symptoms had been present for two years or more, 73 (48 per cent) were subjected to sympathectomy (Fig. 19). This higher incidence in the latter group may be explained by the fact that more severe symptoms were observed in this group.

*Results of Treatment.*—In the past the treatment of postphlebitic sequelae has been largely unsatisfactory, and it is only by a careful study of patients who have been followed for a sufficiently long time that an evaluation of a particular therapy can be obtained. Of the entire 246 patients in this series, all of

Fig. 19.



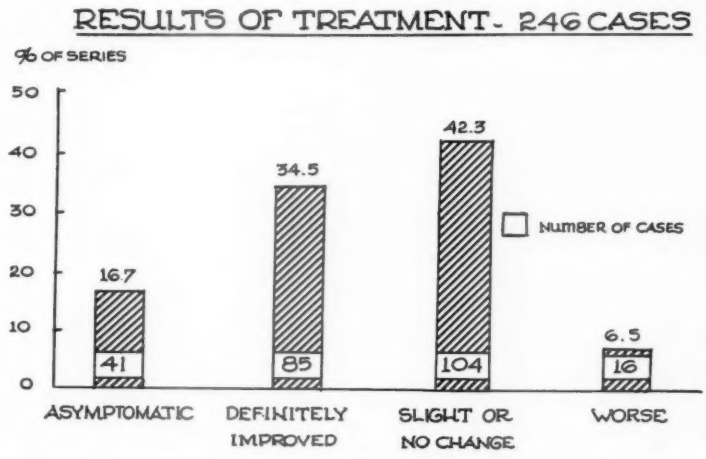
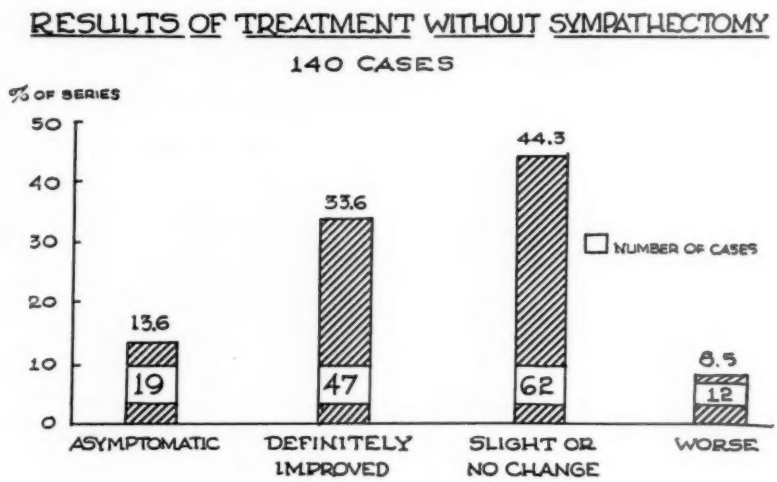




Fig. 20.

whom have been carefully followed, 41 (16.7 per cent) became asymptomatic, 85 (34.5 per cent) were definitely improved, 104 (42.3 per cent) had slight or no change, and 16 (6.5 per cent) became worse in spite of therapy (Fig. 20). In the 140 patients in whom conservative therapy was used, 13.6 per cent became asymptomatic, 33.6 per cent were definitely improved, 44.3 per cent had slight or no change, and 8.5 per cent became worse in spite of therapy (Fig.

21). Of the 106 patients treated by sympathectomy, the results were somewhat better; 22 (20.8 per cent) became asymptomatic and 38 (35.8 per cent) were definitely improved, giving a total of 56 per cent in whom there was definite improvement as compared with 47 per cent of the patients treated conservatively (Fig. 22). Forty-two (39.6 per cent) had slight or no change, and 4 (3.8 per cent) became worse in spite of therapy, as contrasted with 8.5 per cent in whom sympathectomy was not done.

Fig. 21.



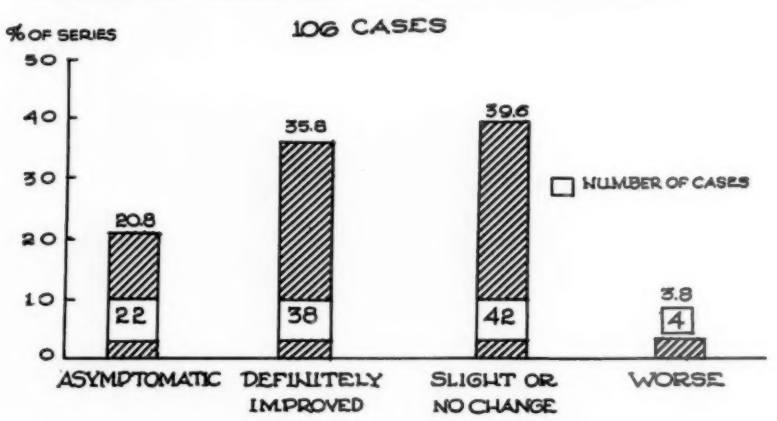
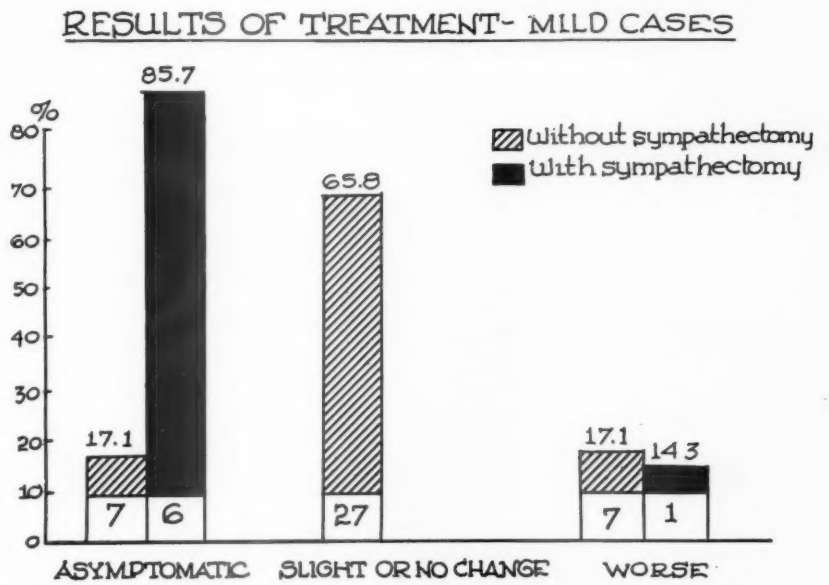




Fig. 22.

Consideration of the results of treatment according to the severity of the clinical manifestations reveals that of 41 patients with mild disease treated conservatively, 17.1 per cent became asymptomatic, 65.8 per cent showed slight or no improvement, and 17.1 per cent became worse in spite of therapy (Fig. 23). Of the 74 patients with moderately severe symptoms treated conservatively, 12.2 per cent became asymptomatic, 39.2 per cent were definitely improved, 41.2 per cent had slight or no change, and 6.7 per cent became worse

(Fig. 24). Of 25 patients with severe manifestations treated without sympathectomy, 12 per cent became asymptomatic, 72 per cent were improved, and 16 per cent had slight or no change (Fig. 25). Seven patients with mild manifestations had sympathectomy. Although this number is too small to justify drawing any conclusions, the fact that 6 (85 per cent) of the 7 became asymptomatic and only one was not benefited is possibly of some import. This appears particularly significant when compared with the results obtained in the

Fig. 23.



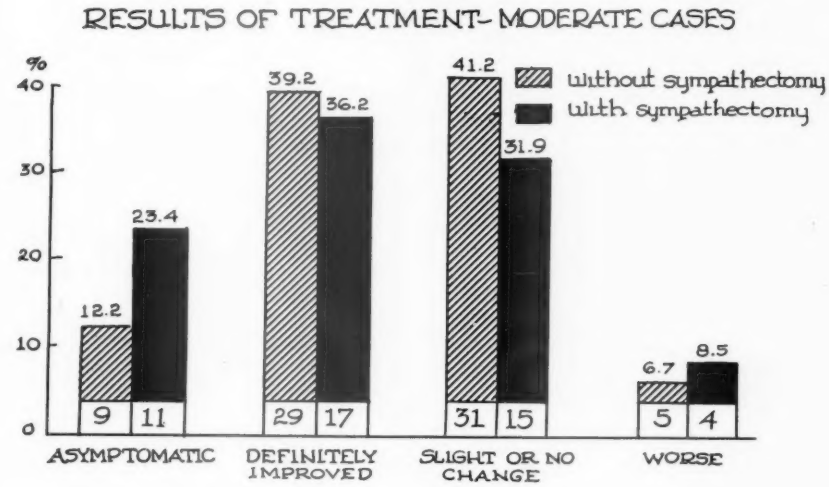




Fig. 24.

patients with mild disease treated conservatively (Fig. 23), in whom 17.1 per cent became asymptomatic, 65.8 per cent were improved, and 17.1 per cent became worse. Of 47 patients with moderately severe symptoms treated by sympathectomy, 23.4 per cent became asymptomatic, 36.2 per cent were defi-

nitely improved, 31.9 per cent had slight or no change, and 8.5 per cent became worse in spite of therapy. These results are also significant when compared with those obtained by conservative therapy in the comparable group in which 12.2 per cent became asymptomatic, 39.2 per cent were improved, 41.2 per cent had no change, and 6.7 per cent became worse (Fig. 24). Of the 52 patients with severe manifestations treated by sympathectomy, all of whom were much worse generally than those treated conservatively because it was considered that the more severe the case, the greater the need or urgency for radical procedures, 9.6 per cent became asymptomatic following therapy, 40.4 per cent were definitely improved, and 50 per cent had slight or no change (Fig. 25). Undoubtedly, in many of these patients more ancillary procedures should have been used in order to have obtained better results. Although the

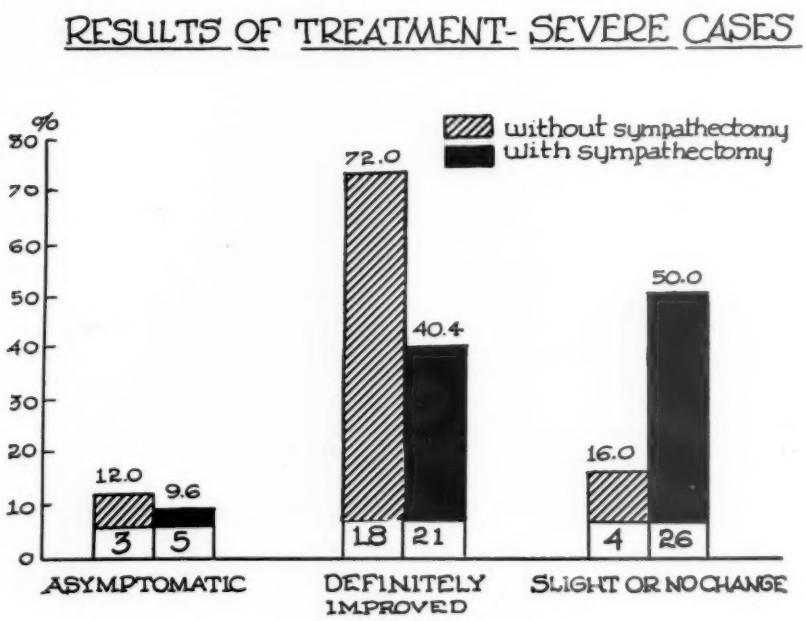



Fig. 25.

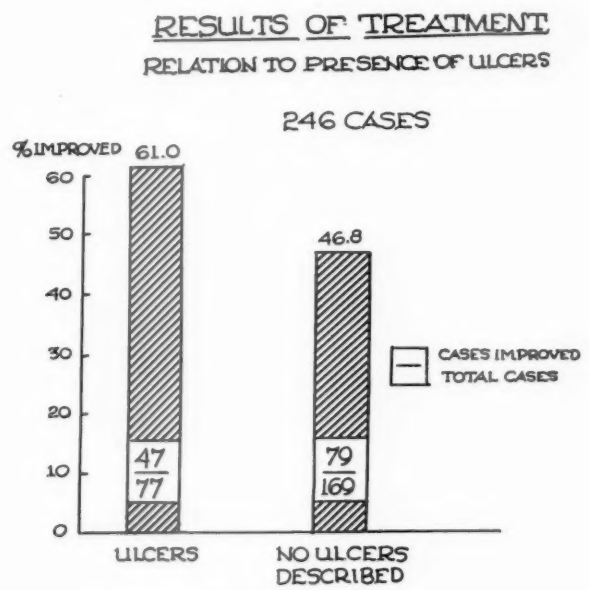
complicating manifestations, such as ulcers and recurrent cellulitis, are undesirable and disabling, their presence does not necessarily indicate that the prognosis is worse. In fact, Buxton and Coller[22] noted that their best results were obtained by deep venous ligation in cases in which ulceration was present and that the results were not good in cases without ulceration. Of the 77 patients in the present series with active or recently active ulcers, 61 per cent were improved by therapy. Of the 79 patients without ulcers, 46.8 per cent were improved by therapy (Fig. 26). Similar results were obtained in cases in which recurrent cellulitis or erysipeloid infection occurred. Of 58 patients with this complication, 53.4 per cent were definitely improved. Of 188 without cellulitis or recurrent erysipeloid infection, 50.5 per cent were improved by therapy (Fig. 27).

Although it might seem likely that the more chronic a condition becomes the less likely it is to respond to therapy, this was not observed in the

present series. Of the 92 patients with symptoms less than two years, 53.2 per cent were improved by therapy. Of the 152 patients with symptoms two years or longer, 50 per cent were improved by therapy (Fig. 28).

This study demonstrated that much can be accomplished by conservative therapy and vasodilatation in persistent postphlebitic sequelae, but the re-

Fig. 26.



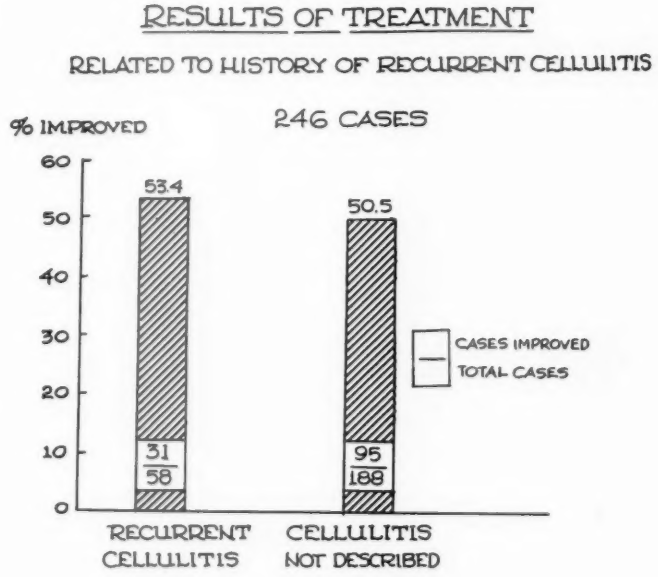
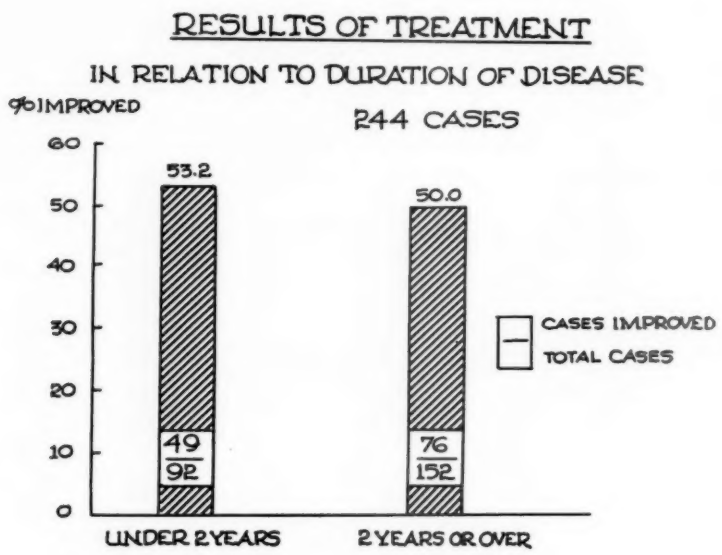




Fig. 27.

sults are far from perfect. Although, as previously emphasized, most of the patients with postphlebitic sequelae have persistent vasospasm because of impulses originating in the thrombotic segment of vein which are carried over

the sympathetic nervous system to the accompanying arterioles, there are some instances in which additional factors are responsible for the production of symptoms. This is particularly true in the patient who does not respond beneficially to procaine block of the lumbar sympathetic ganglia. In such instances, we have attempted to determine whether the deep veins of the involved extremity

Fig. 28.



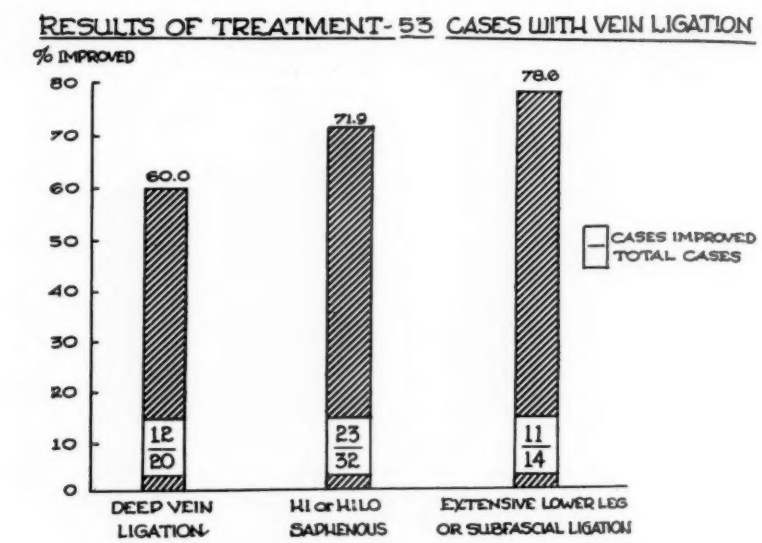




Fig. 29.

are blocked and also whether or not the valves of these veins are incompetent. The former can be determined by phlebography. If the deep veins fail to fill, one can assume that this is due to a persistent thrombus. On the other hand, if the deep veins fill readily, it is obvious that the lumen is not obliterated and in patients who also show no improvement following sympathetic block we

have assumed that failure to obtain relief by vasodilatation is due to the increased venous pressure and stasis resulting from incompetence of the valves of the deep veins. Edwards and Edwards[23] demonstrated that inflammation of the deep veins frequently causes destruction or fixation of the venous valves with subsequent incompetence. Holling, Beecher, and Linton[24] showed that incompetence of the valves of the communicating veins predisposes to edema because of increased venous pressure. Although we made a deductive diagnosis of valvular incompetence indirectly by demonstration of patent deep veins in patients with persistent symptoms after lumbar block, Bauer[25] recently demonstrated incompetence of the valves of the deep veins directly by retrograde phlebography. He exposed the femoral vein in the upper part of Hunter's canal and injected the contrast substance distally with the patient in the head-elevated position. In normal persons the contrast substance will flow distally until it strikes the first competent valve. The phlebogram shows an obstruction at that site. In the patient, however, in whom the valves of the deep veins are incompetent, the deep venous system completely fills even though the contrast substance is injected from above.

Although we have considered that many individuals require supplementary procedures for relief of persistent postphlebitic symptoms, this study has demonstrated that probably more supplementary procedures are necessary. In those instances in which the valves of the deep veins are found to be incompetent, it is desirable to interrupt the deep venous system in some way. Buxton and associates[26] were the first to advocate ligation of the femoral vein in the treatment of postphlebitic ulceration. Homans,[13] Buxton and associates,[22, 26] and Linton and Hardy[18, 19] also employed ligation of the deep veins. Whereas we have usually ligated the superficial femoral vein at its junction with the profunda, Bauer[25] advocated division and resection of the popliteal vein.

In those instances in which there is incompetence of the valves of the communicating veins, particularly in the lower part of the leg, and in which there is the likelihood of a persistent ulcer, subfascial ligation of the communicating veins is essential in addition to ligation of the deep venous system. Linton and Hardy[18, 19] advocated, in addition to ligation of the deep veins (superficial femoral), stripping of the superficial veins in cases with superficial varicosities.

Only occasionally is the deep venous system completely obliterated. It is our belief that in such cases persistence of symptoms is due to an extensive perivascular cicatrix which interferes with the development of both venous and lymphatic collaterals. For persistent postphlebitic sequelae which are not benefited by sympathetic block and in which phlebography shows absence of filling of the deep venous system, we have employed the "unbridling" operation suggested by Jennings,[27] in order to relieve the strangulating effect of the thick, perivascular cicatrix. The extensive perivascular scar is dissected free from the vascular bundle which relieves the constricting effect on the venous system and possibly permits the development of new lymphatic channels.

Other operative procedures aside from sympathectomy were employed in 53 (21.5 per cent) patients in the present series and the results obtained generally have been good. Probably a larger number of patients should have had similar procedures. Of 20 patients in whom the superficial femoral vein was ligated, 12 (60 per cent) were definitely improved. Of 32 patients who had high and high-low ligation of the saphenous veins, 23 (71.9 per cent) were improved and of 14 patients in whom extensive lower leg or subfascial ligation of the communicating veins was performed, 11 (78.6 per cent) were improved (Fig. 29).

*Recurrent Streptococcic Infections.*—Edema, particularly of the lower extremity, is undesirable not only because it is uncomfortable and disabling, but also because it is a potential hazard in predisposing to recurrent erysipeloid infections. Sabouraud[28] and Unna[29] were the first to call attention to the etiologic significance of streptococci in cases of progressive lymphedema associated with erysipelas-like attacks. In 1911 and later in 1913, Matas[30, 31] described the similarity of the clinical picture of recurrent erysipelas and that of acute attacks of recurrent lymphangitis occurring periodically in cases of recurrent lymphedema which terminates in elephantiasis. Drinker and coworkers[32] showed that the persistence of edema favors the development of streptococcic infection. They demonstrated that dogs which normally are resistant to hemolytic streptococci become extremely susceptible locally in the presence of edema resulting from lymphatic obstruction. Because of this, it is imperative that in all persons in whom there is a tendency to develop edema, every measure must be taken to prevent the persistence of edema and the development of the inflammatory process. This can be obviated largely by adequate control of edema by the use of compression bandages and the prevention of streptococcic infection in the edematous area. Streptococci usually gain entrance to the extremity through breaks in the skin and are especially likely to be associated with fungus infections of the feet, such as epidermophytosis. Recurrent attacks of erysipeloid infection produce chills and fever associated with burning, itching, pain, and redness of the extremity. Although edema following uncomplicated thrombophlebitis is relatively easy to control by rest in bed and elevation of the extremity or the use of compression bandages and exercise, the swelling of the extremity associated with, and subsequent to, recurrent erysipeloid infection of the edematous extremity does not subside with bed rest. This is because of the deposition of scar as a result of infection. Although edema is a prominent part of the picture, the edematous fluid is encapsulated in small lacunae formed by dense fibrous tissue and cannot be carried away as normally occurs. In recurrent erysipeloid infection a vicious circle is set up. Edema predisposes to infection which in turn increases the edema because of the deposition of scar tissue and ultimately true elephantiasis results.

The therapy of recurrent streptococcic infection of the lower extremity associated with edema consists primarily of prophylaxis, that is, the control of edema and the prevention of streptococcic infection in patients with incipient edema. The incidence of this condition is much greater in the South,

probably because of the higher incidence of epidermophytosis, resulting from the warm climate and the excessive perspiration of the feet. In many cases, lumbar sympathectomy is advisable in order to produce anhydrosis of the feet and thus prevent cutaneous maceration, epidermophytosis, and streptococcic infection. It must be emphasized that sympathectomy is done in such cases because of the dehydrating effect and not primarily to produce vasodilatation. In order to control incipient streptococcic infection sulfadiazine, 3 or 4 Gm. daily, is given one week each month for one year.[33]

## SUMMARY

1. Postphlebitic sequelae consist of persistent edema, pain, varicosities, ulceration, and recurrent streptococcic infections.

2. In a series of approximately 600 patients, 246 have been carefully followed for six months or longer. The original phlebitis occurred postoperatively in 30.9 per cent, post partum in 16.3 per cent, spontaneously in 12.2 per cent, posttraumatically in 9.3 per cent, and in varicose veins in 3.7 per cent.

3. Persistent postphlebitic edema is due to one of three causes: (1) persistent vasospasm, (2) increased venous pressure due to incompetence of the valves of the deep veins, or (3) extensive perivenous cicatrix. Relief of the edema following vasodilatation suggests that vasospasm is the etiologic factor. If no relief is obtained by vasodilatation, phlebographic studies are indicated to determine the presence or absence of incompetence of the valves of the deep veins and perivenous cicatricial contraction.

4. In the present series of 246 patients, 57 per cent were treated by conservative measures, 43 per cent had sympathectomies, and 21.5 per cent had other radical measures. Sympathectomy was done more frequently in men (41.7 per cent) than in women (38.6 per cent) because disability in a man who is a wage earner is more significant than a similar disability in a woman.

5. Of the 246 patients, 16.7 per cent became asymptomatic, 34.5 per cent were definitely improved, 42.3 per cent had slight or no change, and 6.5 per cent became worse in spite of therapy. The more chronic cases responded as well as those of shorter duration. Of 92 patients with symptoms less than two years, 53.2 per cent were improved by therapy, and of the 152 patients with symptoms two years or longer, 50 per cent were improved by therapy.

6. Although sympathectomy is of value in the treatment of postphlebitic edema due to persistent vasospasm, more radical procedures are necessary in many cases of postphlebitic sequelae.

7. Incompetent valves of the deep veins are an indication for deep venous ligation and frequently subfascial ligation of the communicating veins. The latter is particularly indicated in the presence of ulceration.

8. Recurrent erysipeloid infection can be prevented by controlling the edema and preventing entrance of streptococci, particularly through the feet by the presence of epidermophytosis.

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# THE USE OF ULTRASONIC PULSES FOR THE MEASUREMENT OF BIOLOGIC TISSUES AND THE DETECTION OF TISSUE DENSITY CHANGES

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ULTRASONIC waves, as their name implies, are sound waves of very high frequency. They behave in a manner similar to that of other types of sound waves in that their speed of travel through media varies with the density of the media. Further, ultrasonic waves can be reflected by surfaces or interfaces to produce echoes.

A method for measuring the thickness of the human bowel in situ in the living subject was sought, and the use of high frequency sound waves was deemed feasible. It is the purpose of this communication to describe the results so far obtained.

## PRINCIPLE

The source of the ultrasonic waves is a thin quartz crystal which can be caused to resonate electronically.

The vibrations are produced by thickening and thinning of the crystal. The crystal does not vibrate continuously but is stopped and started electronically. A frequency of 15 megacycles per second was selected as the equipment was at hand. The duration of the pulse was about ½ microsecond (½ millionth of a second), so that in this time about 7½ waves would be propagated. The pulse energy can reach a very high order without danger of destroying living tissues, since the duration is extremely short. The ultrasonic pulses are reflected by "interfaces," that is, surfaces where a change of density occurs. These reflected waves strike the same crystal, and electrical changes occur, much in the same way as crystals used in phonograph pickups. The electrical impulses produced in the crystal are amplified greatly and conducted to the synchroscope, which is synchronized with the transmitted pulses so that the time taken for the echoes to return can be measured. Since this time is a function of the density of the medium through which the ultrasonic waves are traveling, the thickness can be measured if the density of the medium is known. Also, density changes in tissues can be detected.

## THE CIRCUIT

A simplified diagram of the circuit is shown in Fig. 1. The pulse-maker, or trigger unit, times the pulses which are delivered to the crystal by the crystal driver. At the same time a pulse is delivered to the synchroscope, Fig. 2, *A*, which is a device similar to a television screen. Echoes or return signals from interfaces are picked up by the crystal which has stopped vibrating and are sent to the synchroscope via a powerful amplifier. These signals can be displayed as amplitude modulations (deflections from a base line), Fig. 2 (*1*, *2*, and *3*). The images on the synchroscope can be observed with the naked

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eye and photographed. If the density of a given tissue is the same but the thickness varies, the break in the base line will correspond as shown in Fig. 2 (right-hand corner).

### THE APPARATUS

A standard crystal from an Ultrasonic Trainer, Device 15-Z-1, developed by the Special Devices Center of the U. S. Navy, was mounted in a chamber as

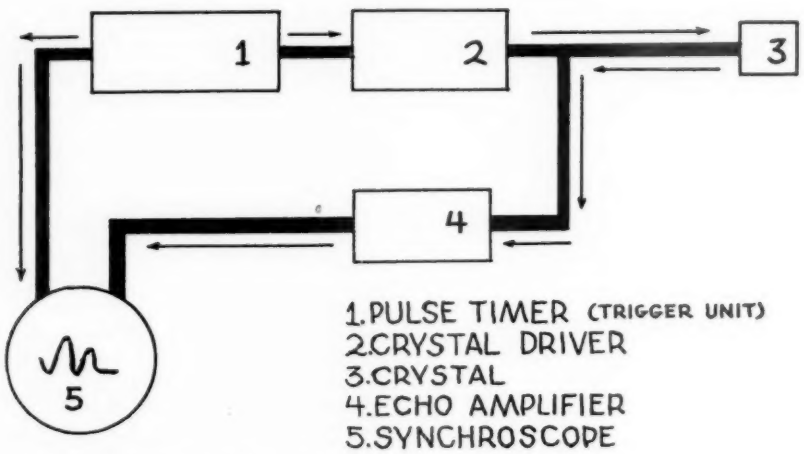


Fig. 1.—The basic essentials of the electronic equipment are depicted. The direction of the various electrical pulses are indicated by means of arrows.

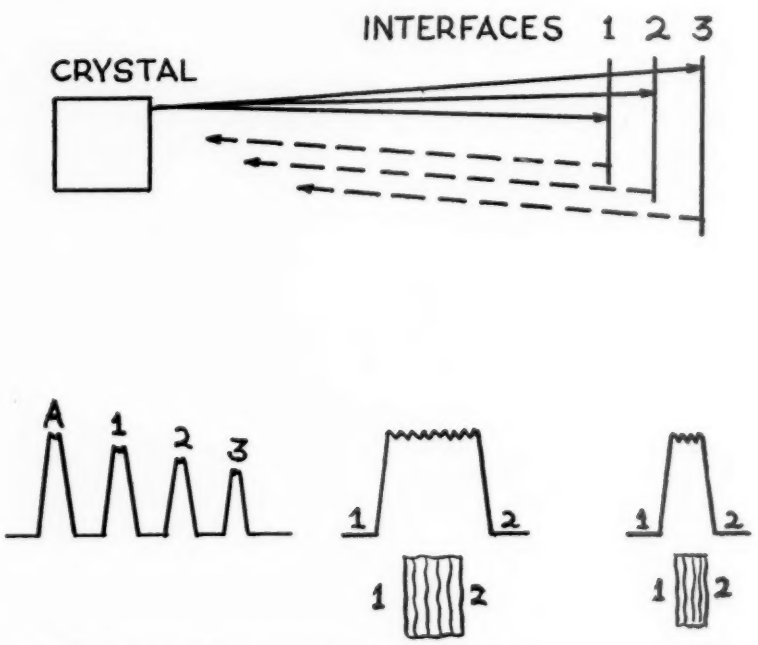


Fig. 2.—A diagrammatic representation of the mode of action of the ultrasonic pulses and echoes is shown in the upper part of the diagram. The hard lines represent the path of one signal only and the broken lines the various echoes returned from the interfaces *1*, *2*, and *3*. The synchroscope picture is shown to the lower left side. *A* is the trigger pulse and *1*, *2*, and *3* are the echoes. On the lower right side is depicted the base-line intervals returned from tissues of differing thickness but of the same density.

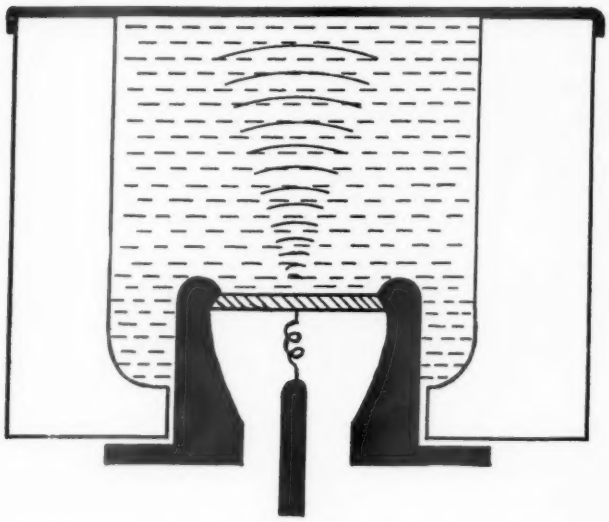

Fig. 3.—The arrangement of the crystal chamber is shown. The mounted quartz crystal was cemented into the base of the chamber which was filled with water. The thin rubber membrane used in some of the experiments can be seen across the top of the chamber.

Fig. 4.

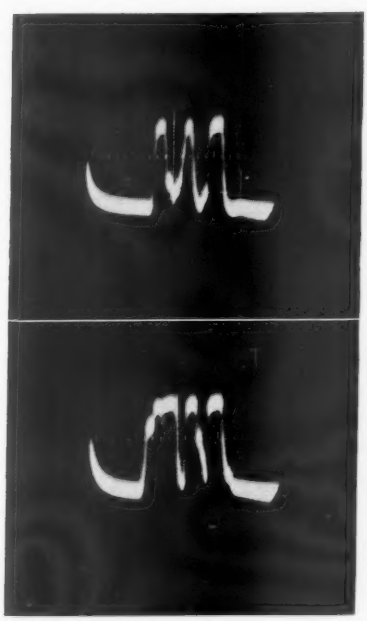

Fig. 5.

Fig. 4.—The echoes returned from three layers of fresh small intestine of the dog can be observed. The rubber membrane was not used in this experiment. The intervals in the base line represent the three thicknesses of bowel.

Fig. 5.—The same experiment as in Fig. 4, but with the rubber membrane in place over the outlet of the crystal chamber, is depicted. The membrane signal can be seen to the left up to the small point in the direction of the base line. The next three peaks are produced by the interfaces.

shown in Fig. 3. This chamber was filled with water and the materials to be tested were placed on top. Since intraluminal gastrointestinal studies were contemplated, a rubber membrane of condom thickness was stretched across the top of the crystal chamber for some of the experiments. The water is used to prevent the crystal from breaking and to dissipate heat.

## EXPERIMENTS

Many experiments were carried out with various types of biologic tissues, and some of the more interesting ones are described here.

The tracing obtained from three layers of the small intestine of a freshly killed dog is shown in Fig. 4. The first layer was placed over the aperture of the crystal chamber in such a way as to exclude air bubbles. Then records were taken of one, two, and three layers. Each layer could be detected as it was laid on top of the preceding layer. The downsweep of the base line to the extreme left is the last part of the trigger unit wave *A* in Fig. 2. The tracing is interpreted as follows:

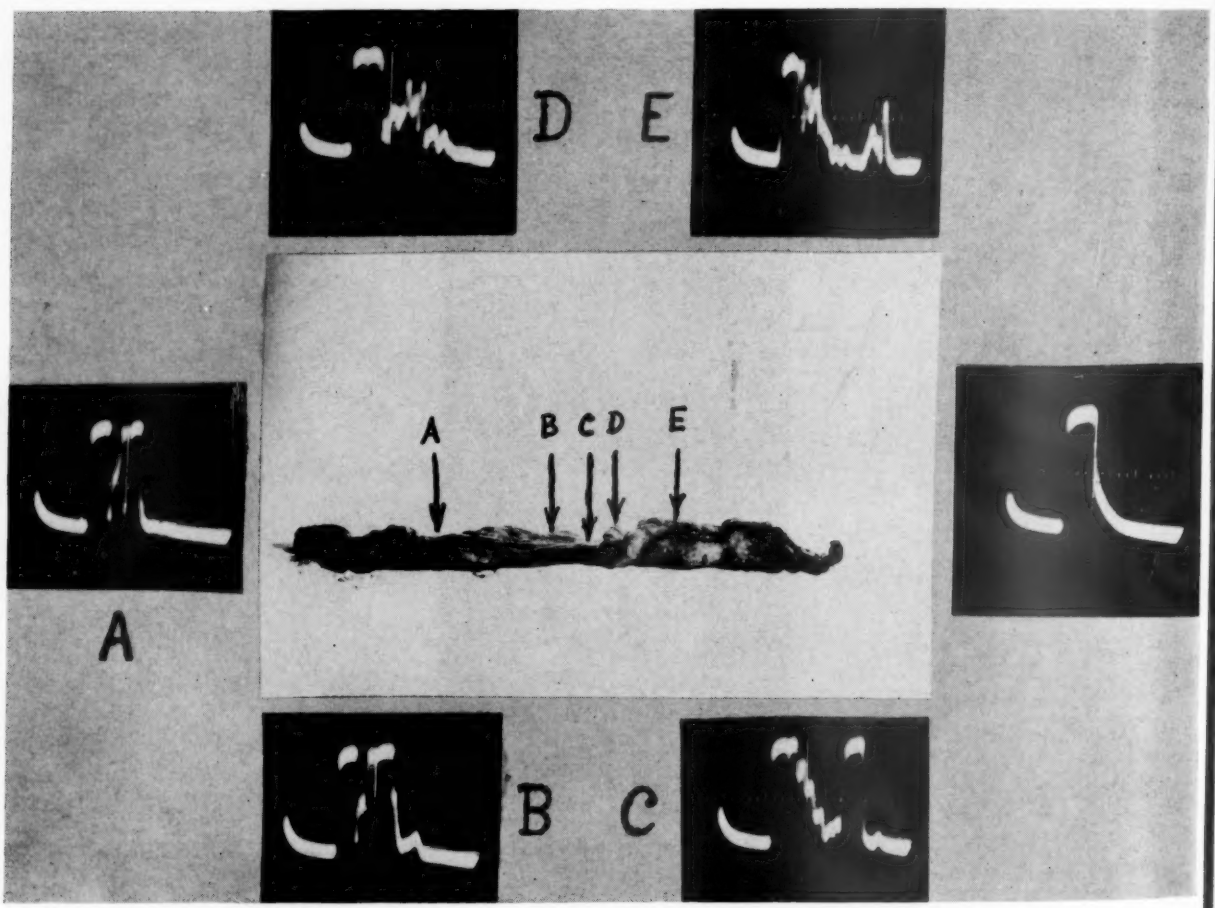


Fig. 6.—The results of experiments with a fresh strip of human stomach containing a carcinomatous ulcer are represented. The alphabetical letters on the central picture of the specimen correspond to those of the synchroscope pictures. The tracing to the right is of the rubber membrane only. The controls of the apparatus were not adjusted between pictures so that all the pictures are comparable.

The first thin upsweep from the base line is the signal returned from the water-bowel interface. The peaks of this first upsweep are the echoes from the bowel substance and the downsweep and upsweep which follows is the first bowel-surface to bowel-surface interface, and so on. The last downsweep to the right is the bowel-air interface. The base line intervals represent the thicknesses of the layers of bowel. The strongly reproduced peak echoes represent saturation of the echo amplifier.

In order to determine the effect of a rubber membrane interposed between the crystal and the object of study, the same experiment with layers of fresh dog bowel was performed with a sheet of condom rubber stretched across the mouth of the crystal chamber. The recorded echoes are shown in Fig. 5. The membrane can be seen to the left of the three peaks as part of the return signals from the first layer of bowel.

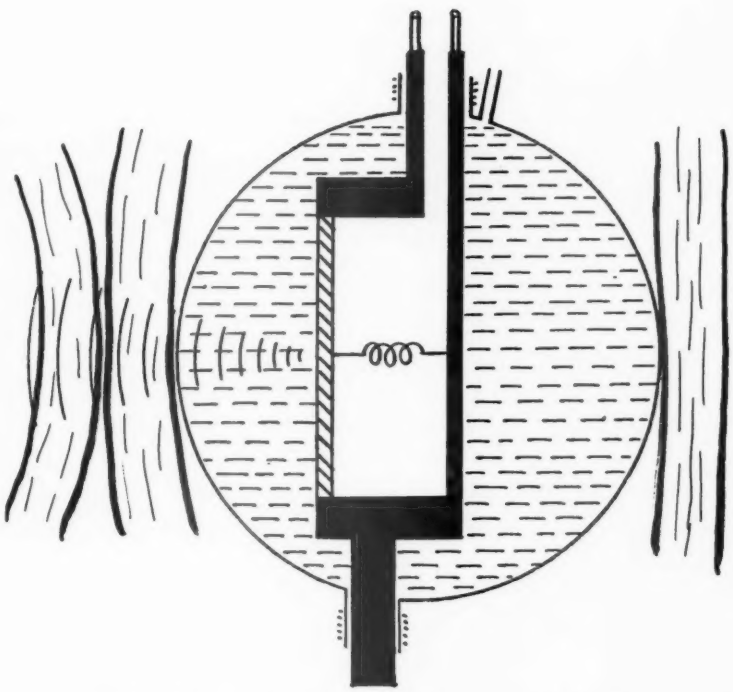

Fig. 7.—The construction of the proposed instrument for intraluminal studies in the human gastrointestinal tract is illustrated.

It was decided next to investigate the signals returned from a tumor mass. Accordingly a strip of human stomach containing a carcinomatous ulcer was obtained from the operating room. A picture of this specimen is shown in Fig. 6. The alphabetical letters pass from normal to infiltrated tissue. The synchroscope tracing *A* shows two strong signal returns from the normal stomach wall. The tracing *B* through the infiltrated area near the ulcer shows a widening of the base-line interval, which indicates a denser tissue, since the thickness of the stomach wall at this point was approximately the same as at *A*. In the region *C* the base-line interval widened still further. The tracings

*D* and *E* taken through the everted edge of the tumor and through the tumor mass, respectively, show not only a still wider base-line interval, but also many interface returns from within the tumor substance.

## DISCUSSION

The application of the principles described here to the investigation of human bowel function would seem a distinct possibility on the basis of the experiments described.

Technical improvements in the apparatus would make possible greater definition of echoes. The type of apparatus for use within the human bowel is shown in Fig. 7.

From the experiments demonstrated in Fig. 6 it should be possible to detect tumors of the accessible portions of the gastrointestinal tract both by density changes and also, in all probability, by failure of tumor tissue to contract and relax.

It is to be hoped that such studies will reveal tumors long before they are detectable by radiologic methods.

For the detection of tissue density changes in other accessible organs of the body, such as the breast, the crystal could be placed next to the skin. The method should be of considerable use in physiologic fields, since contracting tissues can be examined.

## SUMMARY

A method of measuring the thickness of biologic tissues by means of ultrasonic echoes is described.

The method can be applied to the detection of changes in tissue density.

The application of these principles to the detection of accessible tumors is discussed.

*Acknowledgments.*—To Dr. Finn J. Larsen of the Research Division of Minneapolis-Honeywell Regulator Co., who gave constant encouragement and help in the face of technical difficulties.

To Donald Neal, B. of A. E., of the U. S. Naval Reserve, whose assistance and selfless devotion to the work made the experiments possible.

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# PHYSIOLOGIC MECHANISMS OF INTRA-ARTERIAL TRANSFUSION

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ALTHOUGH intra-arterial therapy has received a certain amount of attention in recent years, it is by no means an innovation. In 1883, Halsted's first published paper,[1] entitled "Refusion of Blood," mentioned its use in the treatment of carbon monoxide poisoning, and reference is made to an earlier work of Landois,[2] who preferred intra-arterial to intravenous routes for transfusion. Since then, much has been written on the subject, and most in the last decade, but little investigation has been directed toward a better understanding of the physiologic principles involved. Following the early references by Halsted, little attention was given to the subject apart from a brief report of Davis and associates,[3] who found a transient but definite rise in systemic arterial pressure following the intraarterial injection of hypertonic saline solution in volumes of approximately 20 milliliters. They also stated that control injections of the same volume of normal saline solution produced no elevation of blood pressure in dogs. Kohlstaedt and Page[4] in 1943 published a study of the relative effectiveness of intravenous and intra-arterial transfusion in hemorrhagic shock which showed conclusively the advantages of the latter method. The ratio was 75 per cent recovery with the intra-arterial method and 30 per cent with intravenous. More recently Robertson and associates[5] have shown that under comparable conditions, intra-arterial blood transfusion produced adequate results four times as rapidly as equivalent intravenous measures.

The report which follows is the result of a series of experiments conducted while testing the efficiency of an intra-arterial transfusion apparatus used in University Hospitals. The equipment, designed and assembled by one of us (C. A. H.), for emergency use, may be of interest to those intending to construct a similar apparatus, the component parts of which are readily available. It was considered desirable to analyze the physiologic principles involved in the rapid recovery of experimental animals subjected to hemorrhagic hypotension and intra-arterial transfusion.

## PRESSURE TRANSFUSION APPARATUS

Numerous pressure transfusion sets have been devised, most of which have been simple; several, however, have been quite complicated, utilizing expensive equipment, much of which had to be handmade. After using a temporarily assembled apparatus for patients admitted to the emergency ward, we set about to construct an apparatus easily assembled from ordinary hospital equipment and simple to operate.

The apparatus designed by one of us (C. A. H.) is made up of standard Upjohn bottles, caps, Murphy drips, an aneroid manometer, and glass and

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rubber tubing of standard sizes. Our chief concern was the prevention of air embolism which might occur during the emergency treatment of a severely shocked patient and consequently a two-bottle system was devised which minimizes the possibility of this complication (Fig. 1). Two 1000 milliliter Upjohn bottles are used as reservoirs. Bottle *B* is partially filled with heparinized saline solution, or plain normal saline solution, and this solution is used to fill the distal tubing and evacuate all air. Bottle *A* contains whole blood or plasma. It is not necessary to clear the tubing between bottles *A* and *B*, because all air is trapped in *B*.

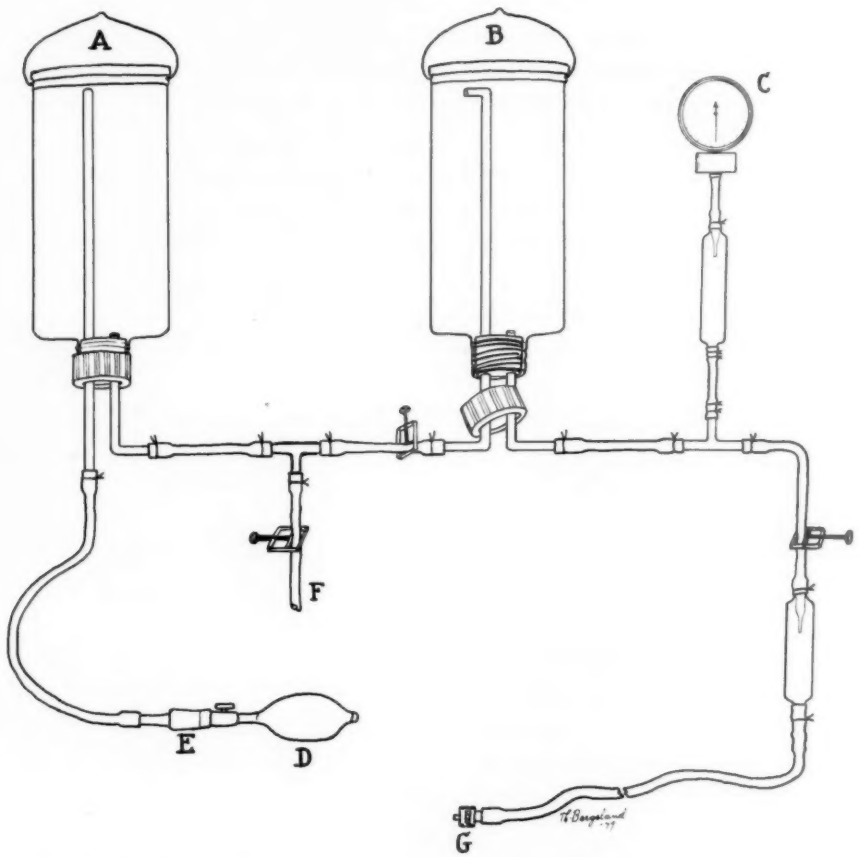


Fig. 1.—Drawing of the apparatus used for intra-arterial administration of fluids. *A*, bottle containing blood; *B*, bottle containing 100 to 200 milliliters of saline solution; *C*, aneroid manometer; *D*, hand bulb; *E*, filter; *F*, T tube for attachment of an additional bottle; *G*, attachment for needle.

Number 5 rubber stoppers with two holes for tightly fitting glass tubing are used in the bottles, and special caps whose tops have been tapped with one inch holes are screwed into the bottles to prevent the stoppers from loosening under pressure. Desired pressure for transfusion is maintained by a hand bulb (*D*), and air is filtered through cotton in an Abbott filter (*E*), or another similar filter. The aneroid manometer (*C*) reads direct pressure in the system when the apparatus is operating at heart level. More blood can be added at T tube *F*. During replenishment enough pressure and fluid remains in bottle *B*

to insure continuous flow. The entire set, with the exception of the aneroid manometer and hand bulb can be readily cleansed and autoclaved and kept in sterile packs. Both intra-arterial and intravenous routes can be used with No. 15 or 16 gauge needles.

### THE LANGENDORF PREPARATION

Langendorf has shown that a mammalian heart, taken from a fresh cadaver and suspended in air at room temperature until all detectable cardiac activity has ceased, will recommence full contractions when the aortic stump is perfused with a physiologic solution of saline under pressure. It is conceded that the perfusing pressure renders the aortic cusps competently shut, directing the perfusing fluid into the coronary arteries.

In our experiments, when a dog is exsanguinated to the point of cardiac and respiratory arrest, the institution of an intra-arterial perfusion raises the pressure in the aorta and the sinus of Valsalva. This constitutes essentially a Langendorf preparation, which permits perfusion of the coronary arteries and the initiation of forceful myocardial contractions. It is presumed that until the ventricular systole generates sufficient pressure to overcome the perfusion pressure, the aortic valves remain closed, and no blood at this stage leaves the left ventricle. After a period of time, usually less than 10 seconds, the normal cardiac cycle is restored and blood again passes from the left ventricle past the aortic valves into the aortic arch.

### THE SINO-AORTIC PRESSURE RECEPTORS

These receptors situated in the aortic arch and at the bifurcation of the common carotid arteries are sensitive to fluctuations of intra-aortic and intra-carotid pressures, and when these pressures are lowered, a reflex peripheral vasoconstriction is effected. It is this mechanism which tends to compensate for hypotensive states up to a certain point by increasing the peripheral resistance, and it is called into play by the process of exsanguination. When intra-aortic pressure rises during recovery the vasoconstriction is revoked, reflex peripheral resistance diminished, and in favorable circumstances normal hemodynamic relationships are restored.

If only partial exsanguination is carried out and the subject left to its own compensatory reflexes, the mechanism would tend to produce normal vascular tone and blood pressure. In ten cases of intra-arterial perfusion of a severely exsanguinated animal, we observed that a high intra-aortic pressure is built up rapidly which is sufficient to revoke the peripheral vasoconstriction, and in addition a steady stream of perfusing fluid is delivered into the arterial tree which, with the restoration of normal vascular tone, produces a rapid perfusion of the capillary networks throughout the body. The results are first, a rapid blood flow through the capillary bed, replacing the previously contained stagnant anoxic blood, and permitting rapid oxygenation of the tissues, and second, a water-hammer pulse. The explanation of the latter may be found in the characteristic pulse found in established aortic regurgitation in man. Textbooks of cardiology attribute the large pulse pressure found in such cases to the peripheral vasodilatation consequent to the large stroke

volume delivered by the left ventricle to offset the residual volume of blood in the ventricle at the end of systole. The vasodilatation is evidenced by the capillary pulsation so frequently seen in these patients.

### RESPIRATORY STIMULATION

When intra-arterial infusion is commenced in dogs exsanguinated until respiratory arrest has occurred, a sudden spasmodic inspiratory effort is produced usually within five seconds and is quickly followed by the reappearance of normal respiration. This was described by Page[6] and adduced by him as evidence of perfusion of the cerebral vessels, more particularly those of the respiratory center. Experiments were conducted by us to determine whether the respiratory stimulus was promulgated by vascular channels or by neural impulses initiated in the arch of the aorta and carried in the vagosympathetic trunk in the dog.

A dog was bled from the femoral artery until respiration ceased. An intra-arterial transfusion was started, and the gasp as described, elicited. Transfusion was continued until normal pressure was re-established. Blood was again allowed to escape until respirations ceased, and at this time rubber shod clamps were placed on the carotid and vertebral arteries. Infusion was instituted, and the usual improvement in pulse and blood pressure noted, but no respiratory gasp occurred, nor did it follow removal of the carotid clamps. When the clamps on the vertebral arteries were removed, the gasp immediately occurred. After first demonstrating that the gasp could be elicited in each dog, similar experiments on eight other dogs were conducted which showed that the gasp was dependent upon the patency of the vertebral arteries and that it could be uniformly produced even when the vagosympathetic trunk on each side was severed.

It was concluded that the respiratory stimulus was the result of increased blood flow through the vertebral arteries, in the dog at least. It was probably initiated through replacement of the static and de-oxygenated blood in the capillaries of the medulla.

### EXCRETION OF URINE

The glomerular filtration of urine ceases when the systemic arterial pressure is progressively lowered by exsanguination. When the pressure drops below an effective filtration level, there exists a specific constriction of the glomerular arterioles.[7] Our observations indicated that in six dogs, this critical level is between 70 to 80 mm. of mercury. If the ureters are cannulated, the flow of urine ceases when this pressure is reached. When intra-arterial transfusion is started, after 30 minutes of hypotension at a level of 40 mm. of mercury, urine commences to flow again within 90 seconds, and before the blood pressure has risen to the critical level. Corcoran and Page[8] have shown that irreversible changes in renal function occur if the period of hypotension exceeds 40 minutes, during which time appreciable renal damage is produced. The duration of hypotension in our experiments thus fell within the limits of reversibility, and the results indicate that during this period restoration of renal function was rapid and indeed was accompanied by a definite diuresis, the volume per minute being as a rule doubled for an

initial period of 10 to 20 minutes. The administration of intra-arterial blood, before irreversible changes had occurred, rapidly established an effective filtration pressure and presumably released the constriction of the glomerular arterioles.

### THE FATE OF FLUIDS ADMINISTERED INTRA-ARTERIALLY

The route taken by fluids introduced under pressure into the arterial tree will vary with the site at which they enter and with the pressure gradient established. For the most part, the radial artery at the wrist has been used in patients, and the femoral artery has been used in experiments on dogs, because its size and accessibility make it more convenient than the rather tenuous radial artery, or slightly larger ulnar artery. Both femoral and brachial arteries have been used in our experiments on dogs, the advantages of the former being its convenience, and also the information which can be derived from a radiographic assessment of the large branches of the aorta lying between the site of perfusion and the heart.

On theoretical grounds, it has been assumed that the ultimate route of the blood introduced is from the site of administration to the arch of the aorta and thence to the coronary arteries, and via the vertebral and basilar arteries to the vital centers in the medulla.

The following experiments were devised to investigate these presumptions by means of angiography. In all instances, dogs weighing 9 to 11 kilograms were anesthetized with intravenous sodium pentobarbital, 0.44 milliliter per kilogram of body weight; and for angiography, 10 milliliters of diiodopyridone acetic acid diethanolamine (Diodrast, 35 per cent) were used. In order to ascertain when the Diodrast had entered the artery, normal saline solution was used as the perfusing fluid, and for accuracy the Diodrast solution was tinged with Evans neutral scarlet. The colored Diodrast was instilled into the delivery tube immediately adjacent to a glass cannula in the femoral artery and prevented from entering, until desired, by a suitably placed clamp. The pressure in the transfusion apparatus was held at 100 mm. of mercury, and approximately 30 milliliters of saline solution were delivered with each portion of Diodrast.

A series of arteriograms was made, commencing with normal blood pressure levels, and at various levels of hypotension, produced by allowing blood to escape from the femoral cannula. The systemic blood pressure was recorded on a kymograph through a cannula inserted in the left carotid artery. During the experiments, every effort was made to ensure that each arteriogram was an accurate representation of the process of intra-arterial transfusion.

*Results.—*

1. With normal systolic pressures of 100 to 110 mm. of mercury, little Diodrast entered the artery, but occasionally it could be shown being forced back into the profunda femoral vessel. No contrast solution reached the bifurcation of the aorta (Fig. 2).

2. When the arterial pressure was lowered to 70 mm. of mercury, the Diodrast progressed much farther into the arterial tree. It filled the aorta

Fig. 2. Fig. 3.

Fig. 4. Fig. 5.

Fig. 2.—Arteriogram through femoral artery. Pressure of infusate 100 mm. of mercury. Systolic pressure 100 to 110 mm. of mercury.

Fig. 3.—Arteriogram through femoral artery. Pressure of infusate 100 mm. of mercury. Systolic pressure 70 mm. of mercury.

Fig. 4.—Arteriogram through femoral artery. Pressure of infusate 100 mm. of mercury. Systolic pressure less than 50 mm. of mercury.

Fig. 5.—Arteriogram through brachial artery. Pressure of infusate 100 mm. of mercury. Systolic pressure 30 mm. of mercury.

as high as the diaphragm, and was shunted into the contralateral iliac, the lower lumbar and renal arteries (Fig. 3).

3. At levels of systemic pressure less than 50 mm. of mercury, it was seen that less contrast material was shunted into large branches of the aorta, in some cases none at all. The most advanced column of Diodrast reached the aortic arch, outlined the aortic cusps, and entered all arteries originating from the arch of the aorta. The coronary and vertebral arteries were visualized (Fig. 4).

4. A similar series, using the brachial artery, showed the same radiographic appearance. Fig. 5 illustrates the filling of the coronary arteries and all the arteries arising from the aortic arch. This experiment was performed when the systemic pressure was 30 mm. of mercury.

These observations indicate that: (1) the amount of infused fluid diverted into branches of the aorta is considerable at normal pressures, but becomes increasingly less as blood pressure diminishes. It is negligible when the systemic pressure is unrecordable. Intra-arterial infusion is thus most effective when the need is greatest, and life most threatened by extreme hypotension.

2. All arteriograms were taken 3 seconds after the infusion was commenced, and the rapid appearance of the Diodrast in the aorta raises the question of the fate of the column of blood previously contained. Its rapid displacement indicates that this volume, being displaced by the infusate, initiates the perfusion of coronary and vertebral arteries.

3. During the course of these arteriographic experiments, it was found that the saline infusion was as efficient in producing the respiratory gasp as was blood, and at first saline solution appeared to produce all the beneficial effects of intra-arterial whole blood.

### INTRA-ARTERIAL ISOTONIC SALINE SOLUTION

A search of the literature produced two early references to the use of saline solution, the first being that of Halsted who recorded a case of shock due to "compound comminuted fractures of the tibia and tarsal bones" successfully treated with "192 cc. of chlor-natrium solution" in September, 1882. Crile,[9] in a discussion of Kloop's paper on blood refusion,[10] mentioned a patient he treated with intra-arterial saline solution which resulted in rapid recovery.

To determine the value of the use of saline solution, further experiments were conducted, using the same principles as with blood, but after exsanguination, saline solution alone was used as the infusate. It was confirmed that saline solution produced the same respiratory gasp and rapid improvement in cardiac function as found when whole blood was used, but differences appeared in the immediate post-transfusion period. Dogs were bled as before until no pulse could be recorded on the carotid manometer. The volume of blood withdrawn was noted and a saline intra-arterial infusion was started. The pressure in the apparatus was held at 100 mm. of mercury. The volume of saline solution administered was equal to that of the blood withdrawn, and when this amount had run in, the infusion was discontinued. The volume of saline solution administered varied from 350 to 500 milliliters in dogs averag-

ing 9 kilograms of body weight. In the period immediately following the initiation of the infusion of saline solution, the response was found to be of the same magnitude and rapidity as with whole blood. When the infusion of saline solution ceased, systemic pressure remained at a level within 5 mm.of mercury of the initial normal level for 5 minutes, began to fall slowly to 65 mm. of mercury at the end of 10 minutes, 40 mm. after 20 minutes, and then was stabilized at 30 mm. for the ensuing one-half hour or more. All dogs so treated died, the longest survival being two hours. When saline solution is replaced by whole blood in this experiment, the normal prehemorrhagic pressure persists indefinitely.

From these observations, it may be seen that saline solution, in emergencies, more rapidly obtained for infusion than suitably typed and crossmatched whole blood, can be used with every expectation of a rapid cardiac and respiratory stimulation and response, but only as an emergency measure until whole blood can be obtained. The importance of this may be emphasized when the extreme susceptibility of the central nervous system and renal parenchyma to anoxia is considered.

Kohlstaedt and Page have reported three patients with extreme hypotension treated with intra-arterial plasma with rapid rise of blood pressure. In each case, intra-arterial whole blood was administered subsequently.

### PRESSURE RELATIONSHIPS

In the manipulation of the intra-arterial transfusion apparatus, the pressure to be established in the apparatus must be considered, for upon it depends the rate at which the infusate is to be administered. The pressure gradient is dependent on the relative pressures in the arterial system. The urgency of the need for treatment will naturally vary from patient to patient, although at present intra-arterial therapy is more often considered when the patient is moribund, or at least in a state of severe hypotension. With wider recognition of the urgency of traumatic and hemorrhagic hypotension and the advantages of intra-arterial infusion, the method may be used with increasing frequency. The immediate need is to stimulate the vital centers and to restore normal levels of systemic pressure as soon as possible, and a rapid rate of infusion appears desirable. One must respect the myocardium which has been subjected to an unknown period of hypoxia and whose functional capacity may be diminished.

Page has advised that an initial pressure gradient of 20 mm. of mercury be established; that is, the pressure in the apparatus should exceed that of the patient by 20 mm. of mercury, this gradient being maintained by raising the infusing pressure at an equal pace with the recovering arterial pressure. Robertson and associates suggested a pressure gradient of 50 mm. of mercury throughout the procedure. In our experiments, the apparatus pressure has been kept at 100 mm. of mercury throughout every procedure, as it was considered that this, approximating normal mean arterial pressure, would allow a rapid flow when hypotension existed, and a progressively smaller flow as the

pressure rose and the need diminished. There was no indication that this pressure was excessive, and at all times the volumes administered were assimilated uneventfully.

The advantages of intra-arterial transfusion have been adequately borne out by the practical application of its methods in cases of shock, and have been amply confirmed by those who have had recourse to its use. These advantages may be briefly summarized as follows: the rapid restoration of circulating blood volume; the immediate response to treatment as shown by the rapid return to normal blood pressure; the specific stimulation of cardiac and respiratory functions when these are failing, and the early re-establishment of renal function. Page has stated that if after intra-arterial transfusion of whole blood the systemic pressure again drops, it is a strong indication of the presence of continued, and perhaps concealed, hemorrhage. Attitudes toward the treatment of hypotension are altered, in that it should be the objective to re-establish normal pressure in a matter of minutes, not hours, and in the intra-arterial route a reliable method of effecting such rapid recovery is available. From the point of efficiency and permanent benefit in hemorrhagic hypotension, whole blood is undoubtedly the first choice, with plasma and isotonic saline solution following, in that order.

## SUMMARY

1. An apparatus for intra-arterial transfusion is described.

2. The physiologic principles of the method are discussed.

3. The mechanism of recovery from hemorrhagic shock with intra-arterial transfusion has been explored by arteriography and by experiments designed to determine the fate of the infused fluids.

4. The possibility of using an intra-arterial saline infusion in an emergency is discussed.

5. The advantages of intra-arterial transfusion are outlined.

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# ACUTE TEMPORARY CHANGES IN RENAL FUNCTION ASSOCIATED WITH MAJOR SURGICAL PROCEDURES

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THE association of various temporary disturbances of renal function and fluid equilibria with anesthesia has been recognized for a half century.[4]

Pringle, Maunsell, and Pringle[6] were the first to study the combined effects of ether and surgical procedures upon the excretion of urine and urinary nitrogen by man. The graphs of Fig. 1 are constructed from their data. The profound suppression of urine and urinary nitrogen during ether anesthesia and the operative procedure led them to write, "We cannot but think that in cases of prolonged ether anesthesia this inhibition of renal activity must exercise a most injurious effect on the general metabolism and condition of the patient."

Following Pringle, Maunsell, and Pringle many others confirmed their observations, but the causes of the urinary suppression remained hidden. Was blood loss a factor? Was water deprivation a factor? Was sodium deficit a factor? Was hypotension a factor? Their data suggest that vomiting, coupled with the inability to drink, prolonged the inhibition of diuresis. However, the experiments of Stewart and Rourke[9] showed clearly, in one case, that the inhibition of water diuresis by ether anesthesia and surgery could not be laid to water deficit because normal rates of urine flow could not be attained for some time after the operation, even though sufficient 5 per cent glucose had been given to reduce the serum sodium and chloride concentrations by 26 and 18.5 mEq. per liter, respectively.

The later studies of Coller and associates[1, 3, 5] confirmed the observations of Stewart and Rourke, although spinal anesthesia was used instead of ether. This is especially significant because spinal anesthesia up to the fifth doral spinal segment is known to be incapable of effecting an inhibition of water diuresis greater than that produced by the spinal puncture alone, provided that no profound fall in blood pressure is induced.

Brief summaries, based largely upon the work of Stewart and Rourke[9] and Coller and associates[3, 5] of some gross changes in renal function attending operations and anesthesia, are given in Tables I to III.

The only important pH regulatory action of the kidney that is significantly depressed during and after a major operative procedure and spinal anesthesia is the differential excretion of chloride, while sodium chloride is being injected.[5] After the operation, when sodium chloride is given, chloride is not excreted significantly faster than sodium and no space is provided for the bicarbonate ion in the saline solution that is retained, and dilutional acidosis may be induced. The normal individual given isotonic sodium chloride excretes chloride sufficiently faster than sodium so that space is provided for the bicarbonate ion in the saline solution which is retained, and consequently little if any dilutional

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acidosis attends the injection of sodium chloride into a normal person. The other pH regulatory actions, namely, ammonia production and the excretion of free organic acids in the urine, are not significantly depressed, provided shock has not been suffered.

The fundamental causes for the changes in renal function associated with a major operative procedure are still unknown, but the number of the possible causes has been reduced. The prolongation of the effect of a general anesthetic agent upon the kidney beyond the point of neural recovery cannot be a primary

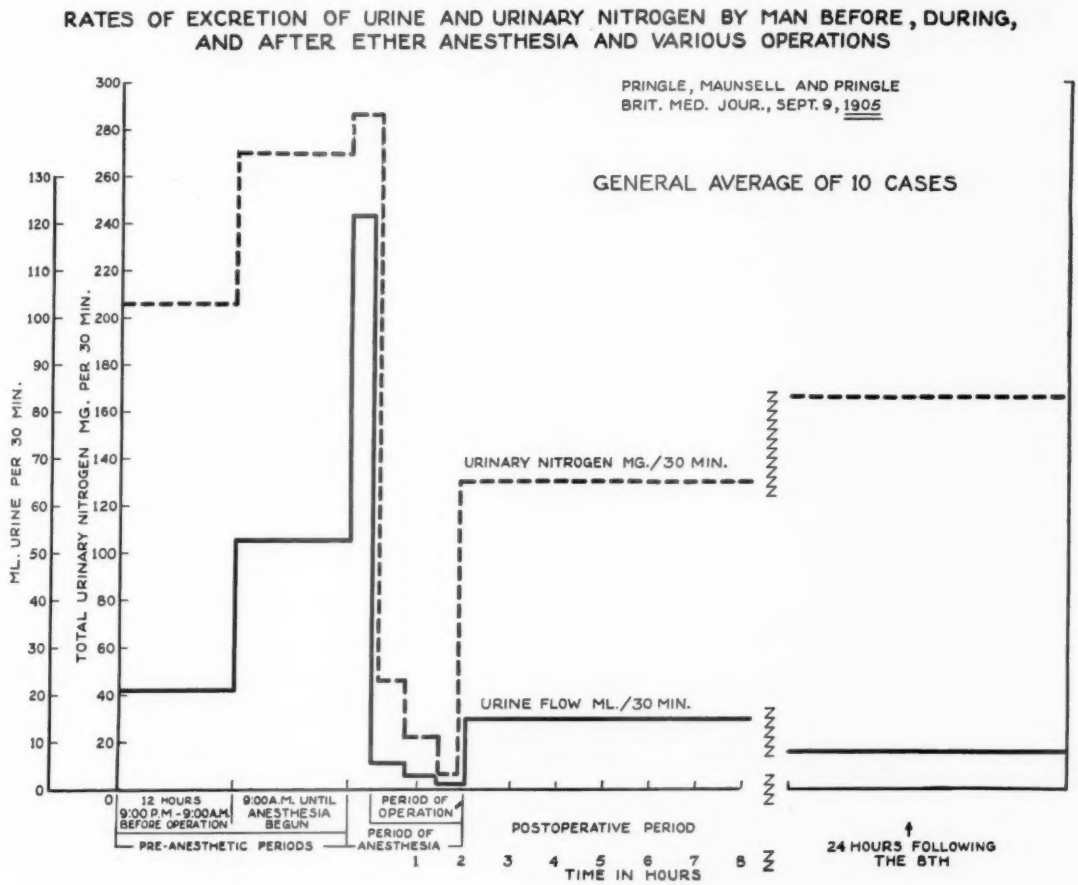
RATES OF EXCRETION OF URINE AND URINARY NITROGEN BY MAN BEFORE, DURING, AND AFTER ETHER ANESTHESIA AND VARIOUS OPERATIONS
PRINGLE, MAUNSELL AND PRINGLE
BRIT. MED. JOUR., SEPT. 9, 1905
GENERAL AVERAGE OF 10 CASES
ML. URINE PER 30 MIN.
TOTAL URINARY NITROGEN MG. PER 30 MIN.
URINARY NITROGEN MG./30 MIN.
URINE FLOW ML./30 MIN.
12 HOURS 9:00 P.M.-9:00 A.M. BEFORE OPERATION
9:00 A.M. UNTIL ANESTHESIA BEGUN
PERIOD OF OPERATION
PRE-ANESTHETIC PERIODS
PERIOD OF ANESTHESIA
POSTOPERATIVE PERIOD
24 HOURS FOLLOWING THE 8TH
TIME IN HOURS

Fig. 1.—A graphic representation of mean excretions of urine and urinary nitrogen by men before, during, and after ether anesthesia and various operations. (The data graphed in this figure were published by Pringle, Maunsell, and Pringle in the British Medical Journal.[6])

factor because normal men anesthetized with ether for one hour, but not operated upon, excrete water and salt in normal ways when given to them as a 0.9 per cent sodium chloride solution intravenously during the anesthetic recovery period. In addition, men anesthetized by the intrathecal route, but not operated upon, suffer no decrement of urinary flow greater than that which attends simple spinal puncture, provided that no profound fall of the blood pressure occurs.[7] And too, when simple operative procedures, such as herniorrhaphy, are performed during spinal or ether anesthesia, significant variations from normal in the renal

TABLE I

| SUBSTANCES INJECTED INTRAVENOUSLY | RATE OF INJECTION INTRAVENOUSLY | RESPONSE OF THE NORMAL KIDNEY (UNANESTHETIZED MAN) | RESPONSE OF THE KIDNEY FOR 24 TO 30 HOURS AFTER SPINAL ANESTHESIA AND A COMBINED ABDOMINOPERINEAL RESECTION OF THE LOWER COLON |
|---|---|---|---|
| 5% glucose in distilled water | 125 ml. per hour | (a) Urine flow increases rapidly so that by the end of the first hour urine is being formed at a rate almost equal to the rate of injection. As a result of this rapid adjustment of the rate of flow of water out through the kidney to the rate of inflow through the needle, there is no significant retention of water and the concentrations of sodium and chloride in the serum remain practically unchanged. | (a) Urine flow increases so slowly so that even by the end of the 24th hour urine is not excreted as rapidly as the sugar water is injected. Consequently, a large amount of the injected water is retained in the body and the concentrations of sodium and chloride fall because the body salts are diluted by the retained water. |
| | | (b) The specific gravity of the urine drops. | (b) The specific gravity of the urine often rises for 12 to 18 hours even though the concentrations of sodium and chloride in the serum fall. |
| | | (c) The concentrations of sodium and chloride in the urine fall rapidly as the diuresis progresses so that by the end of 24 hours only about 1 mEq. of these ions is being excreted per hour. | (c) The concentrations of sodium and chloride in the urine are low (2 mEq. per hour) for 18 to 24 hours and they then begin to rise. |

The above changes are represented graphically in Fig. 2.

responses to saline and glucose infusions are only rarely* encountered.[3, 9] The colligation of these relationships provides evidence that the magnitude of the physiologic impact of the operative procedure itself determines the extent and the duration of the postoperative renal physiologic derangements and that the anesthetic agent per se is not to be implicated except during the actual period of anesthesia.

Since the operation itself appears to be the cause, it is necessary to look into the known fluid derangements associated with the operative procedure. A rapid loss of water as sweat occurs during surgical procedures in overheated operating rooms while the patient is covered with layer upon layer of relatively impervious cloth. As much as 3 liters of a hypotonic salt solution may be lost during a four-hour operation during the summer months. Therefore, a water deficit might be responsible for the postoperative oliguria. It cannot be the primary cause, for when enough water is given during the immediate postoperative period to decrease the concentrations of sodium in the serum and the rest of the extracellular fluid by as much as 10 per cent, the postoperative oliguria still is encountered after major surgical procedures.[5]

*A severe renal functional disturbance in the excretion of water followed a simple dilatation and curettage of the cervix uteri.

The depletion of extracellular sodium during and after the operation, through its external loss and the sequestration thereof into injured tissues, might also be a primary cause of the postoperative renal functional abnormalities which follow major surgical procedures. This possibility can be fairly well ruled out also because the provision of large amounts of sodium with and without an excess of water (sodium as 0.45 and 0.6 per cent saline solutions and sodium as 0.9% saline solution, respectively) does not change the picture appreciably.

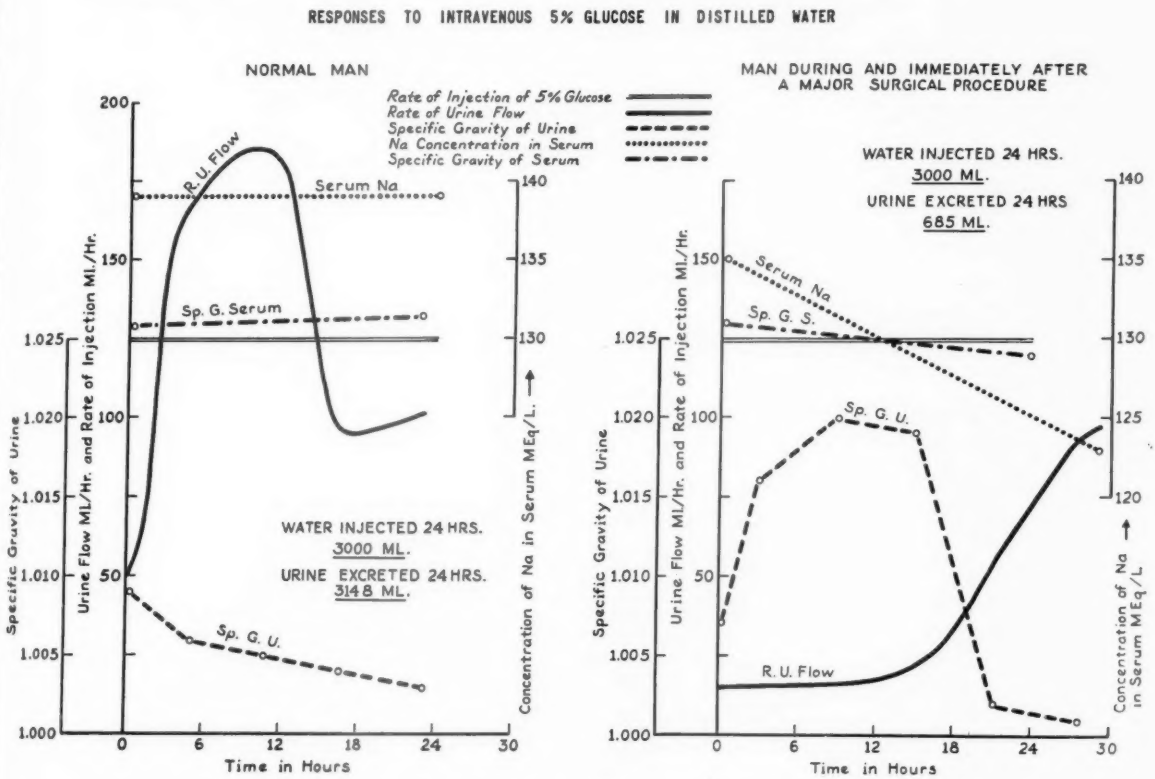
RESPONSES TO INTRAVENOUS 5% GLUCOSE IN DISTILLED WATER
NORMAL MAN
MAN DURING AND IMMEDIATELY AFTER A MAJOR SURGICAL PROCEDURE
Rate of Injection of 5% Glucose
Rate of Urine Flow
Specific Gravity of Urine
Na Concentration in Serum
Specific Gravity of Serum
R.U. Flow
Serum Na
Sp. G. Serum
Sp. G. U.
WATER INJECTED 24 HRS.
3000 ML.
URINE EXCRETED 24 HRS.
3148 ML.
WATER INJECTED 24 HRS.
3000 ML.
URINE EXCRETED 24 HRS
685 ML.
Sp. G. S.
Specific Gravity of Urine
Urine Flow ML/Hr. and Rate of Injection ML/Hr.
Concentration of Na in Serum MEq/L.
Time in Hours

Fig. 2.—The graphs on the left illustrate changes in the rate of flow of urine, the specific gravities of urine and serum, and the concentration of sodium in serum while 5 per cent glucose in distilled water was injected intravenously into normal men at a rate of 125 ml. per hour.

The graphs on the right show the changes in the same variables while 5 per cent glucose in distilled water was injected at a rate of 125 ml. per hour into men and women during and after a combined abdominal perineal resection of the rectum and sigmoid.

(Constructed from previously published data of Coller and associates.[1, 3, 5])

Can blood loss or changes in renal blood flow or vascular paralytic hypotension be implicated? Hardly, because the transfusion of blood at the rate it is lost does not change the picture[3] and the renal inadequacies appear after operations during which hypotension was not suffered,[5] and oliguria attends the infusion of 5 per cent glucose in distilled water during an operation, while the glomerular filtration rate and renal blood flow remain at preoperative normal levels.[2]

What, then, are the factors? There are only two other apparent possibilities: one, poorly understood changes in the kinetics of fluid equilibria associated with trauma, and the other, the inhibition of renal function by painful stimuli

TABLE II

| SUBSTANCES INJECTED INTRAVENOUSLY | RATE OF INJECTION INTRAVENOUSLY | RESPONSE OF THE NORMAL KIDNEY (UNANESTHETIZED MAN) | RESPONSE OF THE KIDNEY FOR 24 TO 30 HOURS AFTER SPINAL ANESTHESIA AND A COMBINED ABDOMINOPERINEAL RESECTION OF THE LOWER COLON |
|---|---|---|---|
| Isotonic (0.9%) sodium chloride in 5% glucose or water<br><br>155 mEq. of Na and Cl per liter | 125 ml. per hour | (a) The volume of urine excreted per hour increases slowly and steadily and very nearly approaches the rate of injection between the 18th and 24th hours usually. | (a) The volume of urine per hour increases very slowly and usually does not even begin to approximate the rate of injection within 24 hours. In other words, the salt solution is avidly retained during and after an operation. |
| | | (b) The relationship of the rate of urine secretion to the volume of saline retained is linear and the ratio $\frac{\text{rate of urinary flow per hour}}{\text{volume of saline solution retained}}$ of different normal individuals varies between 0.07 and 0.7 per hour. The ratio obtaining in a normal person remains relatively constant for long periods of time, up to five years. | (b) The ratio $\frac{\text{rate of urinary flow per hour}}{\text{volume of saline solution retained}}$ is much smaller than normal and varies between .0026 and 0.07 per hour for 24 hours and longer and increases as recovery takes place. |
| | | (c) The salt of the saline solution injected is excreted more rapidly than the water in it. There are 155 mEq. of sodium per liter of saline solution injected, but there is usually more than 220 mEq. of sodium per liter of urine within 12 hours of starting the infusion. In other words, the normal kidney "distills" some pure water from the saline solution. This is very important because distilled water is needed to make up for the insensible loss of water vapor through the non-sweating skin and the lungs. | (c) The salt of the saline solution injected is excreted more slowly than the water in it. There are 155 mEq. of sodium per liter of saline solution injected, but usually there is significantly less than 155 mEq. of sodium per liter of urine for 24 to 30 hours after the operative procedure. Therefore, the body loses some of its water in getting rid of salt and the need for water is increased when isotonic saline solution is given immediately after the operation. The kidney does not "distill" water for the body from the saline solution to supply water for its loss insensibly, but actually increases the need for water. |

The above changes are graphically represented in Fig. 3.

from the operative area. Operations conducted during ether anesthesia are associated with changes of the volume of plasma varying between +3.3 and –33.8 per cent, and alterations in the volume of the extracellular fluid (thiocyanate space) varying between –12.3 and +70.6 per cent of the original volume.[8] No parenteral fluids were given during these studies. It is obvious that an operative procedure may be attended by relatively enormous changes in the distribution of the body fluids and that these changes may be fundamentally responsible for many of the temporary disturbances in renal function following major surgical procedures,

TABLE III

| SUBSTANCES INJECTED INTRAVENOUSLY | RATE OF INJECTION INTRAVENOUSLY | RESPONSE OF THE NORMAL KIDNEY (UNANESTHETIZED MAN) | RESPONSE OF THE KIDNEY FOR 24 TO 30 HOURS AFTER SPINAL ANESTHESIA AND A COMBINED ABDOMINOPERINEAL RESECTION OF THE LOWER COLON |
|---|---|---|---|
| Hypotonic sodium chloride 0.45% | 125 ml. per hour | (a) The rate of excretion of urine usually increases more rapidly than it does when an isotonic salt solution is injected. The rate increases steadily so that by the end of the 12th hour urine is being excreted about as rapidly as the solution is injected. | (a) The rate of excretion of urine increases more slowly than it does in the normal individual but it increases more rapidly than it does when 0.9% NaCl is infused during and after a major operation. The rate of increase is not rapid enough to result in a flow of urine equal to the rate of injection within 24 hours after the operation. |
| | | (b) The specific gravity of the urine falls as the rate of flow of urine increases. | (b) The specific gravity of the urine usually remains unchanged or rises, even though the concentration of sodium in serum falls. In a few instances it falls slightly toward the end of the 24-hour period. |
| | | (c) The water of the solution given is excreted more rapidly than the salt. There are 78 mEq. of sodium in each liter of infusate and for 12 hours or more there are less than 78 mEq. of sodium per liter of urine. Because of this relationship, the concentration of sodium in the serum remains unchanged because the fluid that is retained has been rendered isotonic by virtue of the faster excretion of the injected water than the injected salt. | (c) The water of the solution given is often excreted more slowly than the salt; there are 78 mEq. of sodium in a liter of infusate, but one out of three individuals excretes urine containing more than 78 mEq. of sodium per liter of urine. As a result of this relationship, more water than salt is retained and the concentration of sodium in the serum falls. |

The above changes are not represented in graphic form.

provided that significant deficits of water, protein, or salt; deviations from normal of the concentration of salt in the body; deficits of red blood cells; or hypotension do not exist before, during, or after the operation.

To the role played by these changes in the distribution of body fluids there must be added the effects of painful impulses from the operative area. Minor trauma, such as a spinal puncture, serves to inhibit diuresis,[7] and artificially produced headache inhibits diuresis in man.[11] Studies are now in progress which may delineate the importance of painful stimuli in the causation of the rapidly reversible postoperative functional renal insufficiencies.

Because we do not know the causes of the inhibition of water diuresis and the disturbances of salt excretion that often attend major surgery, we cannot institute active therapeutic procedures to reverse them. However, these renal aberrations attending surgery have postoperative significance. Fluids should

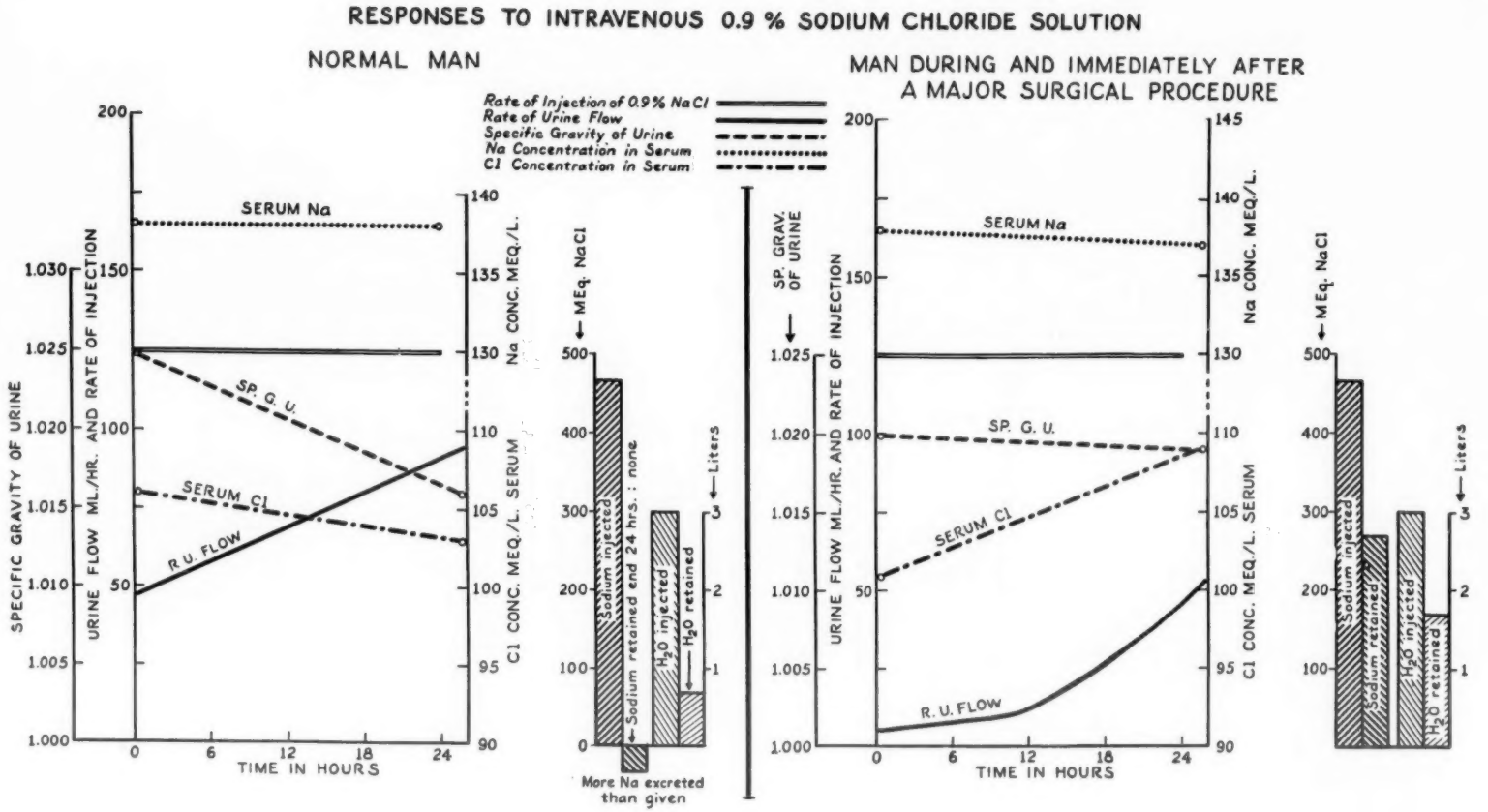


Fig. 3, *A*.—The graphs on the left represent the changes in the rate of flow of urine, the serum chloride and sodium concentrations, the specific gravity of the urine, and the retentions of water and salt while a 0.9 per cent solution of sodium chloride was injected intravenously into normal men at a rate of 125 ml. per hour.

The graphs on the right show the changes in the same variables while a 0.9 per cent solution of *sodium* chloride was injected intravenously into men and women during and after combined abdominal-perineal resections of the sigmoid colon and rectum.

not be given during the immediate postoperative period without taking cognizance of them. The following rough rules take them into consideration:

1. While the period of postoperative inhibition of water diuresis is present, one should not attempt to force a rapid flow of urine by the injection of 5 or 10 per cent glucose in distilled water because of the very real danger of inducing a dangerous intoxication with water.

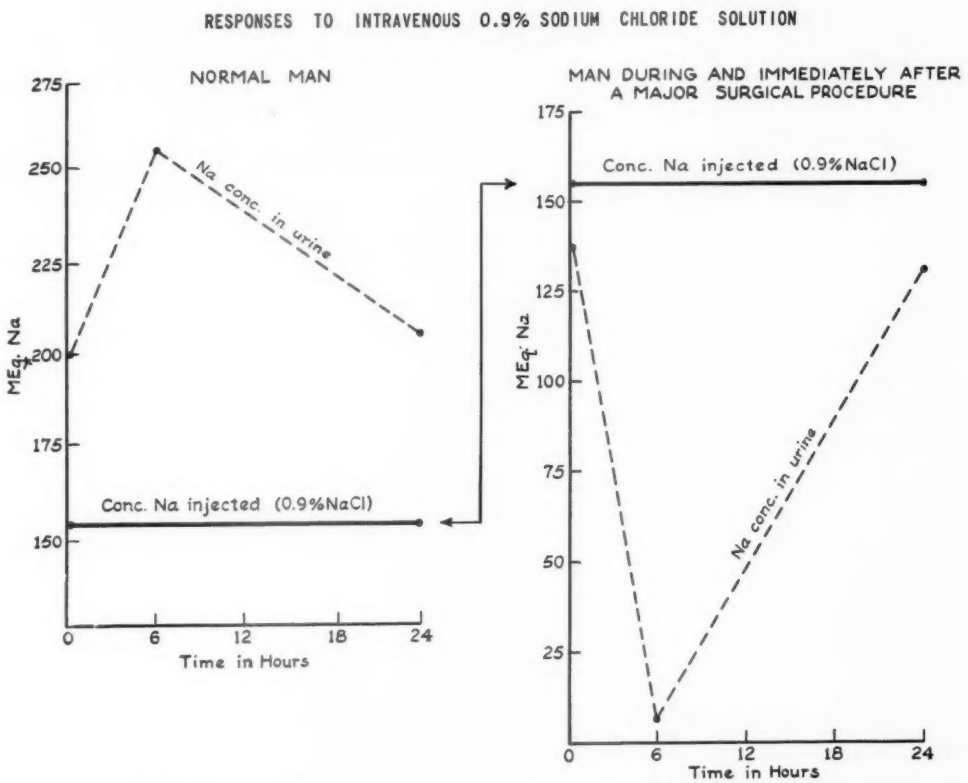


Fig. 3, *B*.—The relationship is graphically shown of the sodium concentrations in the urine to the sodium concentration of the infusate when a 0.9 per cent solution of sodium chloride was administered intravenously at the rate of 125 ml. per hour to normal men, and to men and women who had been subjected to a combined abdominal-perineal resection of the sigmoid colon and rectum.

(Constructed from previously published data of Coller and associates.[1, 3, 5])

The amount of 5 or 10 per cent glucose in distilled water given should only be equal to the need of the individual for *water*. During winter, spring, and autumn, 1,500 to 2,000 ml. per diem is sufficient. During the summer more is needed. In general, for every five degrees Fadrenheit the noonday temperature is above 90 degrees, 1,000 ml. should be added to this figure.

2. Saline solutions should only be given during the immediate postoperative period when there is specific indication for their use: namely, signs of extracellular fluid volume deficit, rapid losses of sodium through suction tubes and fistulas.
3. If saline solution is indicated, a 0.6 to 0.7 per cent solution is preferable to a 0.9 or a 0.45 per cent solution because a 0.6 per cent solution

is not attended by the changes in the concentrations of sodium and chloride in serum that tend to follow the injection of the others.

4. Whenever sodium needs to be given while a normal or a low $CO_2$ combining capacity is present, Hartmann's solution is physiologically preferable to a solution of sodium chloride because Hartmann's solution will not cause the dilutional acidosis that sodium chloride solutions tend to do during the postoperative period when chloride excretion is inhibited. Whenever saline solution needs to be given while a distinctly elevated $CO_2$ combining capacity exists, a solution of sodium chloride is physiologically better than Hartmann's solution (lactated Ringer's solution).

It is evident that the temporary renal functional changes described here are not to be confused with the organic renal complications which occasionally follow an operation and shock; namely, acute tubular nephropathy (lower nephron nephrosis) and acute cortical necrosis.

Finally, attention must be called to the fact that pre-existing or concomitantly developing deficits of water, salt, protein, and red blood cells; disturbances in osmolar concentration of body fluids; and a diminished volume flow of blood through the kidneys aggravate and prolong the temporary disturbances of renal function which so often attend major operations while none of these factors are present. In fact, the occurrence of acute organic disease of the kidney, postoperatively and posttraumatically, may be due to the imposition of these factors upon a kidney, the function of which has been temporarily disturbed by poorly understood changes in the distribution of body fluids, and the effects of painful stimuli.

## SUMMARY

Following major surgical procedures a number of temporary renal functional changes often occur. These changes cannot be ascribed to alterations in renal blood flow, to a deficit of water, to deficits of sodium or chloride, to blood loss, or to the action of the anesthetic agent.

The only apparent possible causes for them are distributional shifts of the body fluids and the afferent stimuli arising in the operative area.

The most prominent temporary renal functional alterations associated with major surgical procedures are: (1) a profound reduction in the rate of excreting water and urea; (2) a severe inhibition in the rate of excreting sodium salt solutions; (3) a reversal of the relationship normally existing between the rates of excreting the salt and the water of sodium salt solutions of varying tonicities; and (4) a reduction in the rate of excreting the chloride that is greater than the reduction in the rate of excreting the sodium of the sodium chloride solution injected. The main therapeutic implications of this list are presented.

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# THE SIGNIFICANCE OF HYPOPROTHROMBINEMIA IN THE NONJAUNDICED SURGICAL PATIENT

## Clinical and Experimental Study

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THE importance of the recognition of low prothrombin content in the blood of the jaundiced surgical patient is well known. The possibility that apparently normal nonjaundiced surgical patients may have lowered prothrombin levels has not been generally recognized. It is the purpose of this paper to report the results of a study on the prothrombin times of 165 consecutive nonjaundiced surgical patients and correlate these findings with the effects of prolonged prothrombin times on wound healing in rats.

To understand the causes of low prothrombin states, one must briefly review the metabolism of vitamin K[1]. Vitamin K is a fat-soluble substance available to the body both by synthesis in the intestinal tract from bacteria and to a lesser extent by dietary ingestion. As with all fat-soluble substances, bile is necessary for its absorption from the intestinal tract. Once absorbed, it is utilized by the liver in the manufacture of prothrombin. Any disturbance in the process of vitamin K absorption or utilization might lead to hypoprothrombinemia.

The possible causes of these disturbances have been well reviewed by Abbott and Holden.[2] (1) Absence in the diet of vitamin K substance, as in the newborn and starvation states; (2) lack of adequate intestinal absorption, that is, intestinal fistulas, short-circuiting operations, intestinal obstruction, prolonged vomiting, intestinal intubation, diarrhea, tropical sprue, celiac disease, ulcerative colitis, etc.; (3) lack of bile in the intestinal tract as in obstructive jaundice or external biliary fistulas; (4) impaired liver function due to any number of causes, including anesthetic agents such as chloroform, barbiturates, and possibly ether.[3-6] We have observed that vitamin B complex deficiency, either frank or subclinical, by producing poor liver function, may lead to hypoprothrombinemia. Recently it has been recognized that the inhibition of growth of intestinal bacteria necessary for vitamin K synthesis by oral chemotherapy, such as the administration of sulfasuxidine[7, 8] and possibly streptomycin, may produce low prothrombin levels. In addition, there still remains a small group of so-called "idiopathic" cases.

That lowered prothrombin levels may lead to deficiencies in the process of wound healing was first suggested by Stewart[9] and D'Ingianni.[10] Since pro-

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thrombin is converted to thrombin, which is utilized for the conversion of fibrinogen into fibrin, lowered prothrombin content of the blood would lead to a lack of available fibrin. Fibrin is essential to the process of wound healing. Ulrich and Lehman[11] showed in experimental animals that disturbance of the coagulation of blood by the administration of heparin caused a delay in wound healing.

## CLINICAL STUDY

For the past year all patients entering on the service of one of the authors (F.I.H.) have had routine prothrombin determinations. These determinations have been done according to the method of Aggeler,[12] using for the most part thromboplastin furnished by him. The technicians performing these tests were adequately trained and the results were reproducible. Prothrombin times of 50 per cent of normal or below arbitrarily were chosen as abnormal, those of 51 per cent or above were classified as normal. As shown in Table I, 13 per cent of the 165 patients in routine admissions presented prothrombin levels considered abnormal.

TABLE I. PROTHROMBIN TIMES OF 165 NONJAUNDICED ROUTINE SURGICAL ADMISSIONS

| PROTHROMBIN TIME | NO. OF PATIENTS | PER CENT |
|---|---|---|
| More than 50% on entry | 144 | 87 |
| Less than 50% on entry | 21 | 13 |

TABLE II. INCIDENCE OF COMPLICATIONS POSSIBLY RELATED TO HYPOPROTHROMBINEMIA IN 162 OPERATIVE CASES

| PROTHROMBIN TIME | NO. OF PATIENTS | COMPLICATIONS | NO COMPLICATIONS |
|---|---|---|---|
| Over 50% | 146 | 4 ( 3%) | 142 |
| Under 50% | 16 | 10 (67%) | 6 |

TABLE III. COMPLICATIONS OCCURRING IN PATIENTS WITH PROTHROMBIN TIMES BELOW 50 PER CENT

| PATIENT | AGE (YR.) | SEX | OPERATION | COMPLICATION | PROTHROMBIN TIME (PER CENT) |
|---|---|---|---|---|---|
| J. S. | 52 | M | Left colectomy, transurethral prostatectomy | Intractable bleeding from both operative sites | 44 |
| R. S. | 61 | M | Gastric resection | Postoperative gastric hemorrhage | 44 |
| M.C. | 75 | F | Excision of rectal polyp | Hemorrhage from operative site, rectum | 23 |
| I. S. | 67 | M | Gastric resection | Intra-abdominal hemorrhage, acute hemorrhagic pancreatitis, leakage from duodenal stump | 43 |
| M. H. | 64 | F | Cholecystectomy | Recurrent acute pancreatitis | 50 |
| O. S. | 63 | F | Excision of recurrent carcinoma of breast | Slough and superficial separation of wound | 22 |
| A. W. | 48 | M | Gastric resection | Hematoma and superficial separation of abdominal wound | 48 |
| J. B. | 75 | M | Cholecystectomy | Superficial separation of abdominal wound, 7 days postoperative | 34 |
| A. D. | 72 | M | Abdominoperineal resection | Evisceration of abdominal wound, 6 days p.o. | 50 |
| H. W. | 42 | F | Subtotal hysterectomy | Evisceration of abdominal wound, 4 days p.o. | 29 |

These two groups of patients were then studied as to the incidence of complications considered as possibly attributable to hypoprothrombinemia, that is, bleeding and failure of wound healing. Wound infections and other unrelated disorders were not included. Prothrombin times were re-determined at the onset of the complications. It is obvious from Table II that whereas complications of bleeding and poor wound healing developed in only 3 per cent of those patients whose prothrombin times were considered normal, 67 per cent of those whose prothrombin times were less than normal developed such complications. Tables III and IV list these complications and the concurrent prothrombin times.

TABLE IV. COMPLICATIONS OCCURRING IN PATIENTS WITH PROTHROMBIN TIME ABOVE 50 PER CENT

| PATIENT | AGE (YR.) | SEX | OPERATION | COMPLICATION | PROTHROMBIN TIME (PER CENT) |
|---|---|---|---|---|---|
| R. J. | 46 | F | Vaginal hysterectomy | Hematuria | 100 |
| J. C. | 41 | M | Thyroidectomy | Hematoma of wound | 62 |
| L. T. | 76 | M | Bilateral inguinal hernioplasty | Superficial separation of abdominal wound | 85 |
| E. S. | 38 | M | Cholecystectomy | Evisceration of abdominal wound, 9 days p.o. | 100 |

It is seen that abnormal prothrombin values are much more frequent than is generally realized and these data are consistent with the thesis that a surgical patient whose prothrombin time is low appears to be more susceptible to complications of hemorrhage and poor wound healing.

In view of the findings on surgical patients which seemed to indicate that poor wound healing and wound disruptions might be related to low prothrombin levels, it was decided to conduct a series of experiments on rats.

## EXPERIMENTAL STUDY

### *Experimental Methods*

*Animals.*—All animals used were female rats of the Long-Evans strain varying between 9 and 18 months of age and 180 and 250 grams in weight. They were fed a complete diet of known composition.

*Collection of Blood.*—According to the method of Campbell and associates,[13] blood for prothrombin determinations was collected by cardiac puncture. Blood, 1.8 c.c., was drawn into a syringe containing 0.2 c.c. of 0.1 M sodium oxalate solution and immediately mixed.

*Prothrombin Times.*—Prothrombin times were determined according to the method of Aggeler,[12] using 50 per cent plasma. The prothrombin times are reported in seconds. Since there was no significant difference between 100 and 25 per cent, a percentage curve could not be established.

*Operation.*—Under ether anesthesia, four wounds were made in each animal; two were on the back and two on the abdomen, staggered in such a way as not to interfere with the circulation. The wounds were carried through the skin and subcutaneous tissues and were sutured with interrupted cotton sutures. The animals were then securely bandaged in order to protect the wounds.

*Tensile Strength of Wounds.*—On the day selected, the animals were again anesthetized and the stitches carefully removed from the wounds. Michel clips were attached to the skin on each side of the wound. The clips were in turn attached to hooks, one of which remained fixed, the other passing over pulleys to a small bucket. Mercury was added drop by drop into the bucket until the wounds separated and the mercury was then weighed.[14]

*Dicumarol Dosage.*—Prolonged prothrombin times were produced by mixing Dicumarol with the food of the animals. The prescribed amount was mixed with 10 Gm. of the stock diet and given to the animals in the morning. When that food was consumed, additional stock diet was given ad lib. Dicumarol in 10 mg. doses was given daily for the first three days, followed by alternating daily doses of 5 mg. and 10 mg.

*Procedure.*—A control series of six animals was first used to determine the prothrombin time on the third day of the special diet. With the dosage schedule outlined here, all animals had prothrombin times prolonged at least to 68 seconds with some being considerably longer.

Next, two groups of rats were operated upon as described. One group was maintained on a normal diet, the other operated upon on the third day of Dicumarol administration. Each group was then subdivided into three groups to be tested on the third, fifth, and seventh postoperative days, respectively.

Prothrombin levels were determined on all animals at the time of testing of the wounds. It is realized that most of the prothrombin levels in the Dicumarol-fed group were much lower than those generally observed clin-

TABLE V

| | THIRD DAY | | | FIFTH DAY | | | SEVENTH DAY | | |
|---|---|---|---|---|---|---|---|---|---|
| | RAT NO. | TENSILE STRENGTH (GM.) | PRO-THROMBIN TIME (SEC.) | RAT NO. | TENSILE STRENGTH (GM.) | PRO-THROMBIN TIME (SEC.) | RAT NO. | TENSILE STRENGTH (GM.) | PRO-THROMBIN TIME (SEC.) |
| Control series | 1779 | 143 | – | 1568 | 197 | 16.1 | 1785 | 228 | 16.8 |
| | 1778 | 108 | – | 1572 | 178 | 14.1 | 1786 | 263 | 16.4 |
| | 1788 | 91 | 15.7 | 1563 | 204 | 14.8 | | | |
| | 1789 | 133 | 15.4 | BH15 | 114 | 16.7 | | | |
| | 1801 | 117 | 18.5 | G06 | 154 | 16.0 | | | |
| Average, control series | | | 117 Gm. | | | 169 Gm. | | | 246 Gm. |
| Dicumarol-fed series | 1787 | 85 | 64.2 | 1781 | 127 | Over 180 | 1783 | 257 | 50.2 |
| | 1798 | 84 | 42.9 | 1790 | 83 | 116 | | | |
| | 1561 | 88 | Over 180 | 1791 | 99 | Over 180 | | | |
| | 1619 | 53 | Over 180 | 1794 | 136 | 110 | | | |
| | 1620 | 78 | Over 180 | | | | | | |
| | 1621 | 89 | Over 180 | | | | | | |
| Average, Dicumarol series | | | 79 Gm. | | | 111 Gm. | | | |
| Dicumarol-fed series with normal or unobtainable prothrombin times | 1780 | 35 | – | 1652 | 144 | 16.1 | | | |
| | 1777 | 133 | – | | | | | | |
| | 1571 | 122 | 14.5 | | | | | | |
| | 1541 | 42 | 24.0 | | | | | | |
| | 1789 | 56 | 16.6 | | | | | | |
| Average 78 Gm. | | | | | | | | | |

ically, but in small animals such as rats it is impossible to control the levels adequately.

Microscopic sections were taken in several of the animals from each group that was tested on the third day, representatives of which are shown in Figs. 1 and 2.

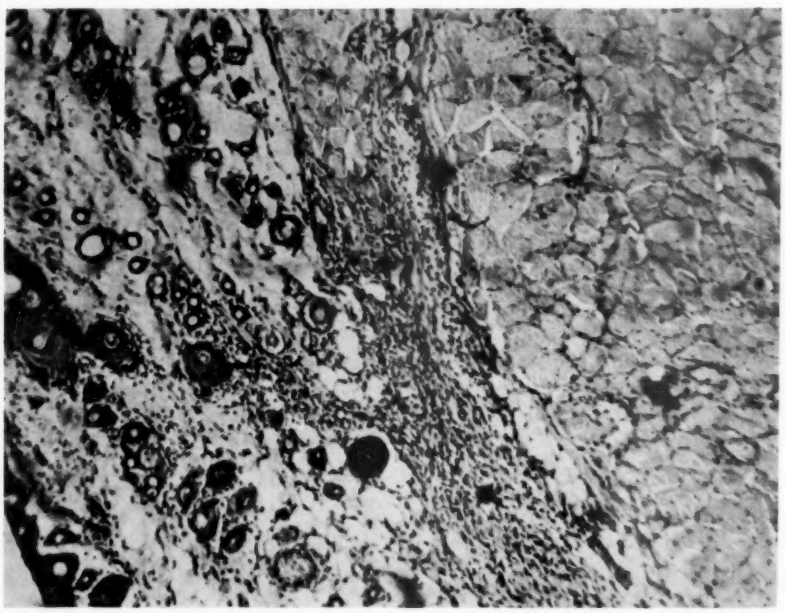

Fig. 1.—Microscopic section of abdominal wound three days postoperatively. Control group.

Fig. 2.—Microscopic section of abdominal wound three days postoperatively. Dicumarol-treated group.

*Results.*—As can be seen in Table V, the average tensile strength of the wounds in the control group is higher, both on the third and fifth days, when compared to the average of the Dicumarol-fed series. This difference is statistically significant (P for both series = 1 per cent). On the seventh day although only one Dicumarol-fed animal was tested, the tensile strength of wounds in each group was essentially the same. The comparison is demonstrated graphically in Fig. 3.

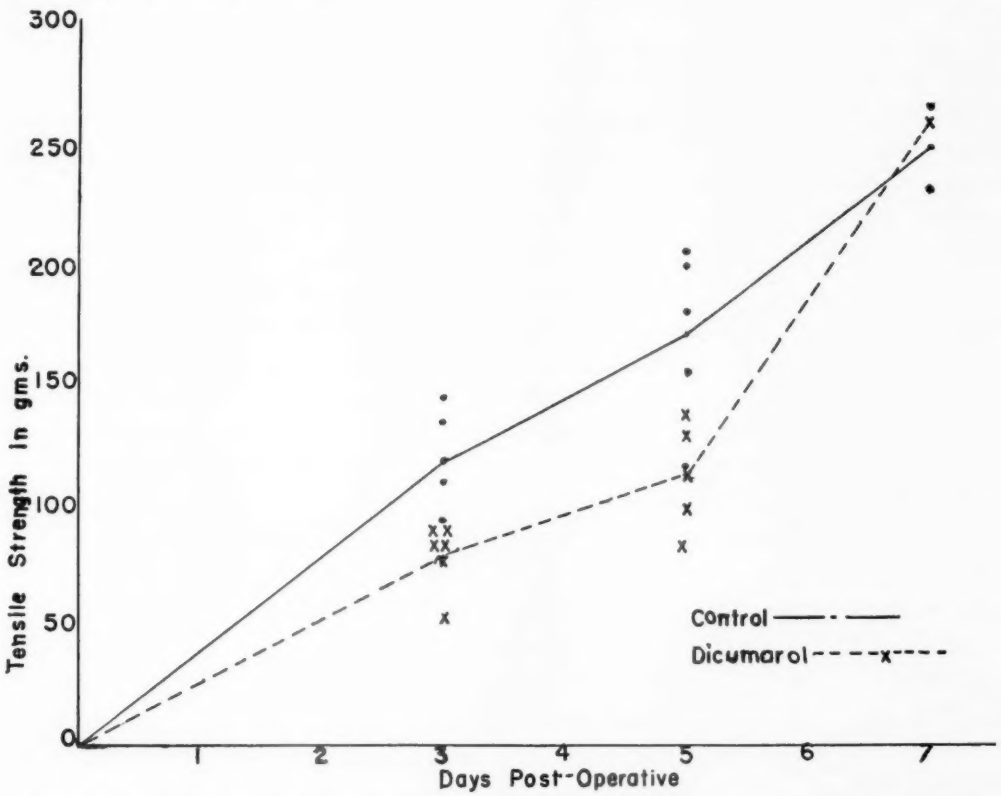


Fig. 3.—Graph showing difference in wound healing in normal and Dicumarol-fed rats.

There was a small group of Dicumarol-fed animals tested on the third day, in which the prothrombin times either were unobtainable for technical reasons or were normal. These are included in Table V but not in the graph. The average of that group is identical to the Dicumarol-fed series with known prolonged prothrombin times.

Some of the wounds of the Dicumarol series showed gross hemorrhage. However, there was no correlation between the amount of hemorrhage and the tensile strength of the wounds; many of the weaker wounds showed no hemorrhage at all.

Microscopic sections from all five animals of the control group (Fig. 1) showed complete epithelial healing, well-progressed organization, a minimum of inflammation, and no hemorrhage. Sections from all five animals of the Dicumarol-treated group (Fig. 2) showed a delay in epithelial healing, a delay

in fibroblast prolifieration, considerably more inflammation, and hemorrhage (in all except one).

## DISCUSSION

The clinical study on nonjaundiced surgical patients who all appeared to be in good nutritional balance reveals a surprisingly high incidence of unsuspected hypoprothrombinemia. It has been suggested that aside from vitamin C or protein depletion, deficiencies in blood-clotting mechanism, secondary to lowered prothrombin levels, may be a factor in poor wound healing. In this study we did not determine the vitamin C or protein levels, but studies are now in progress which eliminate the possibility of these factors.

The study of the complications encountered in these surgical patients and the correlation in the experimental animal strongly suggest that hypoprothrombinemia is a significant factor in delayed wound healing and wound disruption. The experiments of Ulrich and Lehman with heparin, showing a delay in wound healing, substantiate these impressions.

It is possible that hypoprothrombinemia is an early index of a poor nutritional status and that the complications encountered in the patients may be a reflection of generally poor nutrition. The patients in our series, however, demonstrated no clinical evidence of impaired nutrition. In those cases in which a certain degree of impairment of nutrition is present, vitamin B complex and crude liver as well as vitamin K may be necessary to restore the prothrombin time to normal.

Lowered prothrombin levels also bear special importance in surgical patients in view of the recent trend toward the use of Dicumarol in the treatment of postoperative thromboembolic diseases.

It is our belief that routine prothrombin times on the nonjaundiced as well as the jaundiced patient and the adequate treatment of hypoprothrombinemia, when present, may serve to eliminate or at least reduce the incidence of postoperative complications related to hemorrhage and deficient wound healing.

## SUMMARY

1. The metabolism of vitamin K and the known possible causes of hypoprothrombinemia are discussed.

2. A tentative explanation for impairment of wound healing secondary to lowered blood prothrombin content is given.

3. Clinical study of 165 nonjaundiced surgical patients shows a high incidence of unsuspected, low blood prothrombin content. The relationship of low levels of blood prothrombin to postoperative complications such as hemorrhage and deficient wound healing is suggested.

4. Experiments on rats give added evidence that hypoprothrombinemia may contribute to impaired wound healing.

5. Dicumarol therapy during the first postoperative week should be undertaken only with full consideration of the serious surgical complications that might ensue.

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# INVOLVEMENT OF THE PENIS BY CARCINOMA OF THE RECTUM

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INVOLVEMENT of the penis by malignant disease arising in the rectum is apparently quite rare, for only three cases have been found in the literature. The first case was reported in 1933 by Niewiesch[1] in a 69-year-old man who complained of priapism and upon whom a resection of the rectum for adenocarcinoma had been performed. The penis, the corpora cavernosa of which were filled with tumor, was amputated ten months before the patient's death. The second case was reported by Mathesan[2] in a 72-year-old man who had a colostomy performed for carcinoma of the rectum. Within one month metastatic nodules involved the penis so extensively as to compress the urethra and cause complete urinary retention. He died from metastases five months later and it was demonstrated at autopsy that adenocarcinoma of the rectum had involved the penis. In 1937 Stein and Hantsch[3] added a third case in a 62-year-old man who had developed priapism and had noted the appearance in the penis of nodules which on biopsy showed metastatic adenocarcinoma of the rectum. He received x-ray therapy but died within four months from metastases. In view of the comparative rarity of this condition a fourth case is reported.

## CASE REPORT

Mr. F. K. (S.M.H. 162569), a white man, aged 70 years, was seen in the Emergency Department on Nov. 3, 1946, complaining of difficulty in voiding and rectal pain. For a number of years, the patient had had frequency, urgency, and decrease in the size and force of the urinary stream. Several weeks before admission, he had noted gradually increasing nocturia, frequency, and burning pain in the lumbar and in the bladder region. He also experienced fleeting knifelike pains in the rectum, painful defecation, and occasional rectal bleeding. He denied hematuria or pyuria. For five days previous to admission, voiding became increasingly difficult so that only small amounts of smoky urine were passed at the time of urination. Bowel movements had been every other day with the frequent use of cathartics as long as he could remember. There had been no bowel movement for three days prior to admission. The day before admission, he had taken an enema and had noted bright red blood in the returns. No change had been noted in the size or caliber of the stools. His appetite had remained good, and yet he had noted a weight loss of about ten pounds. He had not experienced abdominal pain or distention. His physician on examination found a rectal mass and referred him to the hospital with a diagnosis of cacinoma of the rectum.

At 17 years of age he had had pneumonia. In February, 1940, he had developed a thrombosis of the left popliteal artery and a mid-thigh amputation had been performed with good results. At that time he was found to have a mild diabetic condition which was adequately controlled by a dietary regime. In March, 1940, he had fallen, fracturing the right femur. With skin traction this healed over a period of two months.

Family history and system review were noncontributory.

Physical examination disclosed a well-developed and well-nourished 70-year-old, white man, showing no evidence of recent weight loss. Blood pressure was 180/96. He did not ap-

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pear acutely ill. Bilateral shotty axillary glands were palpable. A well-healed, mid-thigh amputation stump was present on the left. The chest was emphysematous and without intercostal movement. Râles were heard at the right base and in the axilla. The heart was enlarged to the left and downward. The sounds were of good quality with the regular rhythm except for an occasional dropped beat. Peripheral arteries were sclerotic. The abdomen was distended and the bladder was palpable up to the umbilicus. The liver, spleen, and kidneys could not be felt. The neurological examination was in order. On rectal examination, the sphincter tone was good, tenderness was present, and a few internal hemorrhoids were felt. About 3 cm. above the sphincter, on the anterior rectal wall, a circular lesion about 4 to 5 cm. in diameter with rolled and indurated margins was felt. Although its edges were movable, the central crater of the mass was fixed to the prostate. The prostate was markedly enlarged.

The patient was admitted on the medical service with the diagnosis of carcinoma of the rectum, cardiac failure, diabetes mellitus, and acute retention; the latter due either to benign prostatic hypertrophy, or to invasion of the bladder by the rectal tumor. A genitourinary consultation was requested.

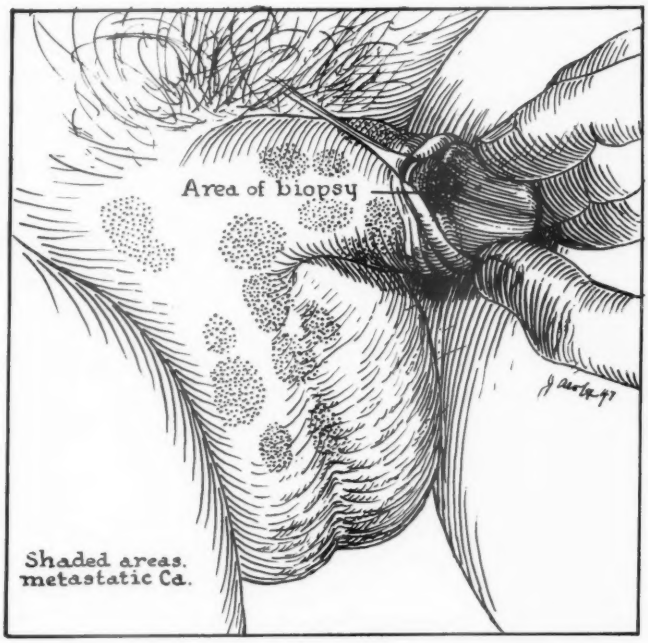


Fig. 1.—Schematic representation of the tumor nodules in the penis and the area biopsied.

Examination at that time revealed a hard, fixed, circular nodule about 1 cm. in diameter on the dorsal surface of the glans penis near the corona. Marked phimosis was present and visual inspection of the nodule was impossible. Extending back along the course of the urethra and involving both the spongiosum and the cavernosa, were numerous, isolated, hard nodules which varied in size from 1 to 1.5 cm. In the region of the bulbous urethra, a large, hard nodular mass involved the ventral aspect of the penis (Fig. 1). The testes and cords were essentially negative. The bladder was palpable above the umbilicus. Rectal examination confirmed the previous findings, except that the prostate could not be differentiated as such, and no true evaluation of it was possible. An attempt was made to catheterize the patient, but a few centimeters inside the meatus, an obstruction was encountered. The patient was taken to the operating room on the night of admission and a suprapubic cystostomy was performed. A dorsal slit was made and a biopsy specimen was taken of the nodule in the glans penis. The pathologic report was metastatic adenocarcinoma in the glans penis, probably from the rectum (Fig. 2).

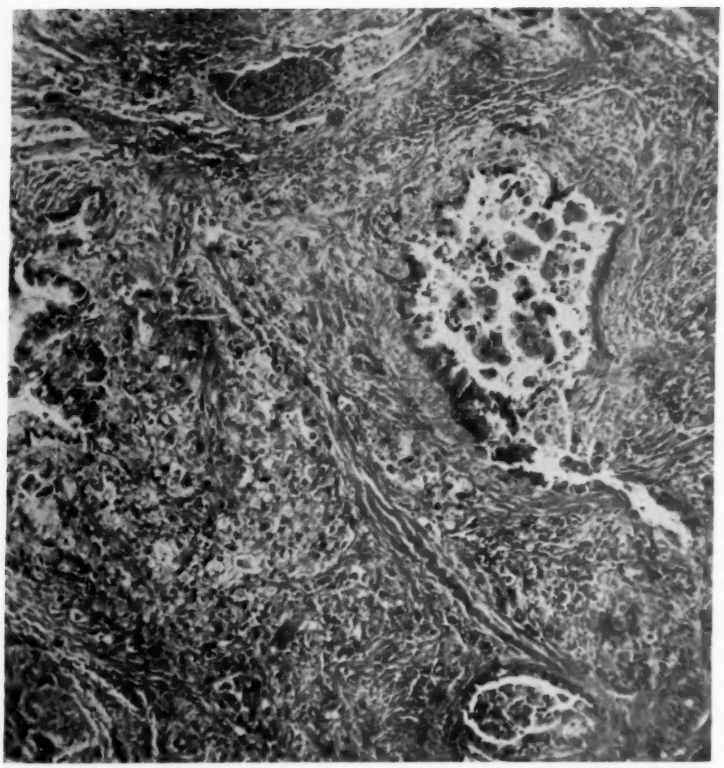

Fig. 2.—Tumor cells in the biopsy specimen from the glans penis.

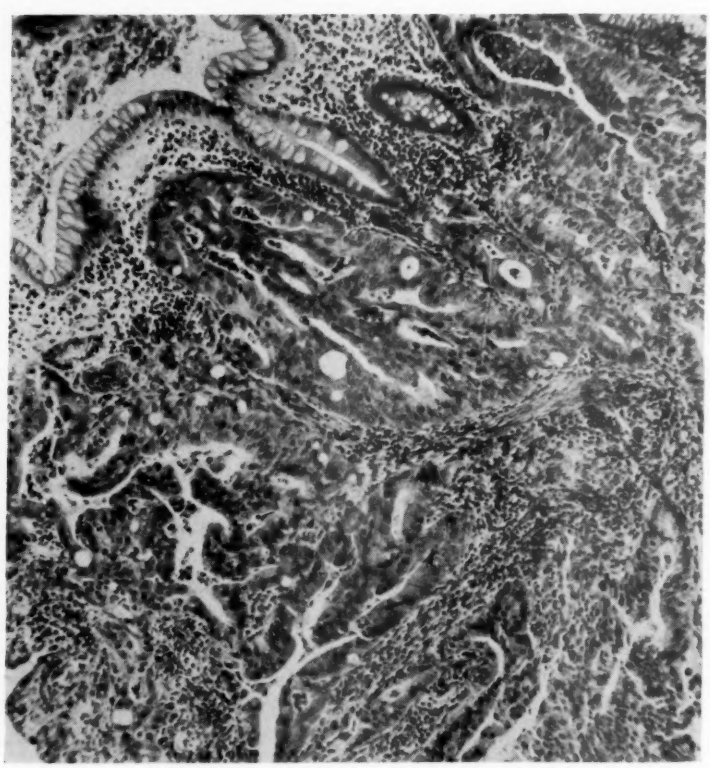

Fig. 3.—Adenocarcinoma of the rectum.

*Laboratory Findings (Postoperative).*—The examination of the blood showed, red blood cells 4,500,000, hemoglobin 14 Gm. per 100 c.c., white blood cells 12,000. The differential count was 90 per cent neutrophils, 10 per cent lymphocytes, and platelets were adequate. The specific gravity of the urine was 1007 and 1 + albumin and 1 + sugar were present. Microscopically the urine showed a few epithelial cells, few white blood cells, and 50 to 60 red blood cells per high power field. Stool was dark brown, guaiac negative. Nonprotein nitrogen was 41 mg. per cent. The fasting blood sugar was 156 mg. per cent. Acid phosphatase was normal but the alkaline phosphatase was 6.7 Bodansky units. Roentgenogram of the chest showed emphysema and old pleural adhesions. Roentgenogram of the pelvis revealed an old fracture of the right hip and degenerative osteoporotic changes consistent with the patient's age.

His postoperative course was uneventful. The suprapubic tube drained well. The biopsied region in the glans penis remained an open ulcerating lesion. A proctoscopic examination on the sixth postoperative day revealed a rolled, irregular, hard, nodular, erythematous edge of a large, irregular, ulcerated mass occupying three-fourths of the rectal wall 1 cm. above the white line at six o'clock. Only the left posterior rectal wall was not involved. The base of the ulcer was gray, necrotic, and bled easily. The mass appeared to be fixed, and completely covered the proximal portion of the prostate. The pathologic report was adenocarcinoma of the rectum (Fig. 3).

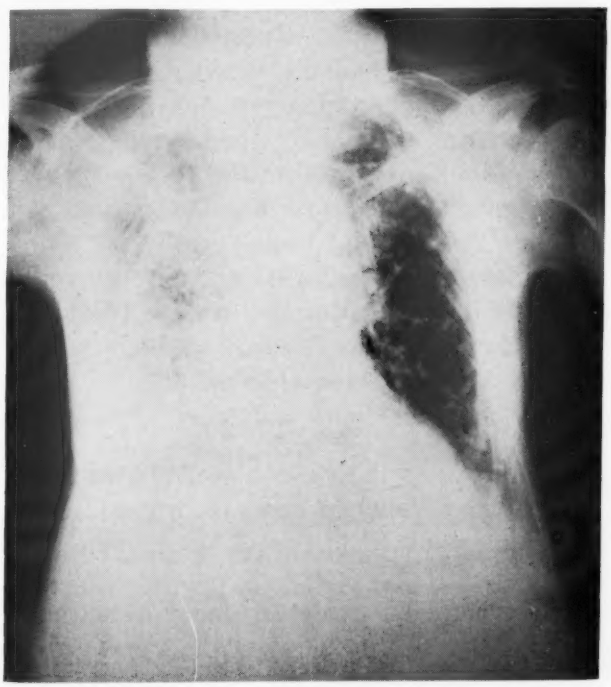

Fig. 4.—Chest x-ray reveals metastastic tumor nodules and bronchopneumonia.

It was felt that the elevated alkaline phosphatase was most likely due to liver involvement by the tumor. He was given a palliative course of x-ray therapy through four portals of 10 by 15 cm. at 7 cm. distance screened by 0.5 mm. Cu and 1.0 mm. Al, amounting to 3,200 r. He was discharged on the twenty-first postoperative day.

He was readmitted two and one-half months later on Feb. 5, 1947, on the medical service with a temperature of 38.2° C., pulse 124, and respirations 36. A diagnosis of bronchial pneumonia with pulmonary congestion due to cardiac failure and probably pulmonary metastases was made (Fig. 4). His course was gradually downhill, and he died quietly on March 13, 1947, approximately four months after the original admission.

At necropsy, adenocarcinoma of the rectum was found with metastases to the lungs, liver, right kidney, prostate, urethra, penis, and heart. The bladder was not involved. The prostate, which was moderately increased in size, was bound down to the rectum, and it was impossible to separate it as a discrete organ. Its posterior and lateral lobes, particularly those areas adjacent to Denonvilliers fascia, were diffusely hard and gray-white and gray striations extended to the urethra and surrounded it. The urethra was quite firm. The seminal vesicles were also bound down to Denonvilliers' fascia, although not as securely as the prostate. The penis when opened had a firm, fibrous corpus spongiosum urethrae that extended back to the bulb. Due to the presence of numerous gray-white nodules, the corpora cavernosa were irregular throughout, although sections through them revealed some fairly normal vascular spaces. The rectum which was bound posteriorly to the sacrum was very tightly adherent to the prostate and the vesical neck. The mucosa lying anteriorly against the prostate and the bladder had a 5 by 6 cm. shallow ulcer with slightly rolled, moderately hard edges, and a center that was covered with a dirty, gray-brown exudate. There were only a few, somewhat hard nodes in the perirectal tissues. Pathologic sections showed invasion of the prostate but not of the seminal vesicles. The urethra showed extensive infiltration, and the penile urethra revealed extension of tumor cells through the corpora cavernosa. Sections of the rectum revealed adenocarcinoma.

## DISCUSSION

Stein and Hantsch,[3] in their discussion of the routes taken by rectal neoplasms, expressed the opinion that involvement occurred by direct extension into either corpus cavernosum by way of the ischiorectal fossae and then through the junction of the deep and superficial ligaments with Colles' fascia into the superficial perineal space. By this route, the cells do not spread against fascial planes. In the event that the corpus spongiosum is involved, the extension would probably have to take place through the urogenital diaphragm.

In our case, it is assumed that the latter had occurred. Microscopic sections revealed extensive infiltration of the urethra beginning in the prostatic region and involving the corpora cavernosa. Whether we were dealing with extension or metastasis could not be established.

## SUMMARY

1. A case of carcinoma of the rectum secondarily involving the penis is reported. This brings the number of cases recorded in the literature to four.

2. Priapism, which was noted in two of the reported cases, was absent in this case.

3. This patient developed complete urinary retention as did one other recorded case.

4. All patients have had bowel symptoms, but only in this one did the urinary symptoms predominate.

5. In three cases the course was rapidly downhill, terminating fatally in four to five months. One patient lived ten months.

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# PRODUCTION OF CHRONIC ENTERITIS AND OTHER SYSTEMIC LESIONS BY INGESTION OF FINELY DIVIDED FOREIGN MATERIALS

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THE fact that so-called inert foreign material, such as sand, in a finely divided state can be absorbed from the digestive tract to the detriment of the organism is not generally appreciated. The experiments reported here were undertaken to determine if sand or talcum powder can be absorbed from the intestinal tract of the dog and, if absorbed, to determine what effect such absorption might have upon the structure and function of the tissues.

Interest in this problem was stimulated by the report of Reichert and Mathes[17] who produced pathologic changes indistinguishable from those of regional enteritis by injecting the lymphatics of the small bowel mesentery of dogs with finely divided sand and other sclerosing solutions. If such pathologic changes can be produced by placing finely divided sand into the lymphatics of the mesentery, the question arises as to whether such material placed into the lumen of the gut would be absorbed with production of a granular lesion.

Efforts to identify a specific bacterium as the etiologic agent for regional enteritis have been unsuccessful. Some investigators think that the tubercle bacillus is the cause of the disease because the pathologic findings are quite similar to those of tuberculosis.[18] On the basis of clinical and experimental evidence, the following organisms, agents, or conditions have been suspected: bacteria (*Escherichia coli, Bacillus dysenteriae,* and all other organisms which are capable of inhabiting the intestinal tract either normally or in pathologic states), bacterial toxins, animal parasites, viruses, allergy, sarcoid, achylia gastrica, foreign bodies, blockage of lymph channels, impairment of blood supply, trauma, appendical inflammation, neurotropic disturbances, hormone imbalance, and vitamin deficiency. Among predisposing factors, as in ulcerative colitis, anxiety and emotional instability seem to be important.[2]

The work of Reichert and Mathes[17] and the negative bacterial studies suggest that factors other than infection may play a part in the pathogenesis of regional enteritis. This is in accord with the work of Pumphrey[16] and Coffey.[4] Coffey commented on the presence of "a crystalline material" in the foreign body giant cell of the lesion. It was theorized, therefore, that if silica particles can be absorbed by the lymphatics of the lung to produce the disease of silicosis, the lymphatics of the intestine should be able to take up silicious material more easily since intestinal lymphatics are developed for the purpose of absorbing substances from the lumen of the bowel. This thought might be applied especially to the terminal ileum where the lymphatics are relatively more numerous

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than elsewhere in the digestive tract and where, because of the presence of the ileocecal valve and the normally occurring reverse peristaltic waves, there is a delay in the passage of intestinal contents.[1, 15]

## MATERIALS AND METHODS

Thirty-seven dogs and twelve rats were used in this work. Twenty-two of the dogs were operated upon for the purpose of making a Thiry fistula, thirteen were given finely divided sand in the daily ration, and two were given talcum powder. Two of the sand-fed dogs were placed on nitrogen metabolism studies and after these were completed, one of these dogs, together with another sand-fed dog, not taking part in the metabolism study, was given injections of bacteria intravenously. One of the dogs fed talcum powder in the ration was also given injections of bacteria intravenously. Of the twelve rats, six were given finely divided sand in the daily ration and six were used as controls.

Of the dogs operated upon, thirteen had talcum powder, U.S.P., placed into isolated loops of terminal ileum; eight, finely divided sand; and one, quinine. In an attempt to visualize the intestinal lymphatics, one of these dogs received a fatty meal with Nile blue, and another, a fatty meal with sudan III, several hours preoperatively.

Microscopic slides of tissues from bowel wall, mesenteric nodes, liver, and lung were studied under the polarizing microscope to determine the presence of birefringent crystals.

*Operative Procedure (Thiry Fistula).*—An ileo-ascending colostomy with isolation of a segment of terminal ileum and cecum was accomplished under morphine and nembutal anesthesia. Into this isolated loop was injected either a suspension of No. 200 to 400 mesh sand and water, or a suspension of talc, U.S.P., such as is used in the operating room to powder surgical rubber gloves. The amount of suspension used was about 10 c.c., which represented either one-half sand and water or one-half talc and water by volume. This quantity was found to produce slight tension in the isolated loop of bowel when a mass ligature was used to occlude the ileal opening after the injection. Care was used not to contaminate the peritoneal cavity with talc during the surgical procedure or during the injection of the isolated loop. The injection was made after the abdomen was closed. These dogs were sacrificed at varying intervals of time up to one year and studied for gross and microscopic pathologic changes.

*Sand Feeding.*—To the standard ration of ten healthy dogs, 10 Gm. sea sand and 10 Gm. No. 200 mesh sand were added, thoroughly mixed with the food, daily. One month later No. 400 mesh sand was made available. This then was substituted for the No. 200 mesh sand. These dogs were sacrificed at intervals up to nearly one year.

*Talc Feeding With and Without Intravenous Injections of Bacteria.*—To the standard ration of two healthy dogs, 10 Gm. talc, U.S.P., were added, thoroughly mixed with the diet daily. Six weeks later when it appeared that the dogs would die, one was sacrificed. The other one recovered and the talc feeding was continued for three months. The dog was observed for an additional four-month period after which an injection of bacteria was given intravenously.

This consisted of a mixture of twenty-four hour cultures of streptococcus, *Staphylococcus aureus,* and *Esch. coli* organisms. Each slant culture was washed with 2 c.c. of physiologic saline solution to make a total of 6 c.c., 2.5 c.c. of which was injected intravenously. The following week 6 c.c. were given, and twenty-four hours later the dog was sacrificed.

*Sand Feeding and Metabolism.*—A healthy dog (No. 12) was placed in a metabolism cage on a standard diet which was analyzed during a control period of one week as to nitrogen and fat balance. Fecal fat and urinary and fecal nitrogen were determined. Nitrogen in the food was determined by the micro-Kjeldahl method with direct nesslerization.[9, 10, 11] Fat content in the food was determined using a Soxhlet method. Fecal fat was determined similarly. Fecal nitrogen and urinary nitrogen were determined by the micro-Kjeldahl method mentioned.

After a control period of one week, 10 Gm. No. 200 mesh sand were added to the same diet daily and thoroughly mixed with the food. The weight of the dog was recorded weekly and the nitrogen and fat analyses were continued for a period of thirteen weeks. The dog was then given an intravenous injection of bacteria as described previously for one of the talc-fed dogs.

Another dog (No. 13) was subjected to a metabolism study as described for Dog 12 with the exception that the control period was extended for six weeks during which time no sand was fed with the diet. The study was continued for an additional five weeks during which time 10 Gm. No. 200 mesh sand were mixed with the daily ration. The daily ration consisted essentially of horse meat calculated to keep a dog in nitrogen balance and furnishing approximately 80 calories per kilogram of body weight per day.

After this study was completed the dog was continued on the standard dog diet with sand added for a total of seven months at which time it was sacrificed with nembutal given intravenously, and the tissues were studied for gross and microscopic change.

*Sand Feeding and Intravenous Injections of Bacteria.*—One dog (No. 11) which had been fed a standard diet to which was added 10 Gm. sea sand and 10 Gm. No. 200 mesh sand daily for three months was given a mixture of a twenty-four hour broth culture of beta streptococci, a twenty-four culture of *Staph. aureus,* and a twenty-four hour culture of *Esch. coli* intravenously. Rectal temperature was taken and spinal fluid examination was made on the second day following the injection of bacteria shortly before death occurred. The death of this dog is attributable to the use of broth cultures which were used in this case instead of saline washings of slant cultures as were used for the other animals given bacterial injections intravenously. Necropsy was done and the tissues were examined for gross and microscopic change.

*Sand Feeding in Rats.*—Two groups of rats, six in each group, composed of thirty-day old litter mates, having an initial average weight of 67 Gm. each, were fed the same basic diet containing 20 per cent protein and 10 per cent fat. Of this diet, 100 Gm. furnish 409.3 calories.

Both groups of rats were fed this same basic diet which was found to maintain normal growth. In addition to the basic diet the six rats in Group 1 were

given 2½ per cent No. 200 mesh sand thoroughly mixed with the food and the six rats in Group 2 were given 2½ Gm. celluflower per 100 Gm. of diet in addition to the basic diet as outlined.

Each day the amount of food consumed was calculated from the known amount given and the amount left unconsumed. The rats were weighed daily and their weights were recorded.

## RESULTS

Of the eight dogs operated upon for the purpose of injecting a suspension of sand and water into a blind loop of gut, none died as a result of the operation. No adverse systemic effects were observed in these dogs. One was sacrificed by an intracardiac injection of nembutal six days postoperatively but before any sand or other agent was given. No significant gross or microscopic changes were observed in the isolated loop of ileum and cecum or mesenteric lymph nodes.

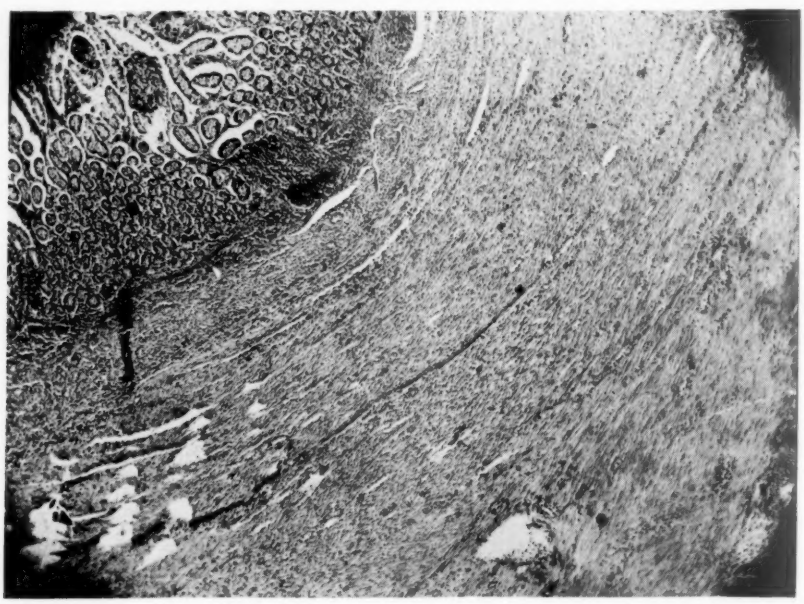

Fig. 1.—Photomicrograph showing a low-power cross section of the bowel wall of the terminal ileum which had been isolated from the fecal stream operatively in the manner of a Thiry fistula, and into which had been injected a suspension of finely divided sand. Note the thickening of the layers.

The remaining seven dogs were fed sand and were sacrificed in the same manner 13, 22, 25, 30, 92, 110, and 210 days after operation. In all of these, gross and microscopic changes were observed in the isolated loop of terminal ileum and in the adjacent mesentery and mesenteric nodes. Grossly there were adhesions between the isolated loop of bowel and adjacent structures. The terminal ileum was thickened and hard (Fig. 1), and its lumen diminished about one-third as compared to its original diameter. A typical measurement at the time of sacrificing the animal was ½ cm. as compared to a diameter of 1½ cm. of the adjacent normal ileum (Fig. 2). Microscopically lymphoid hyperplasia of the submucosa (Fig. 3), and hyperplasia of the mesenteric nodes were noted. A summary of pathologic changes will be presented later in this paper.

Of thirteen dogs similarly operated upon and treated except for the fact that a suspension of talc, U.S.P., was used in place of sand, only four survived longer than 8 days. One died 22 days following operation. The remaining three

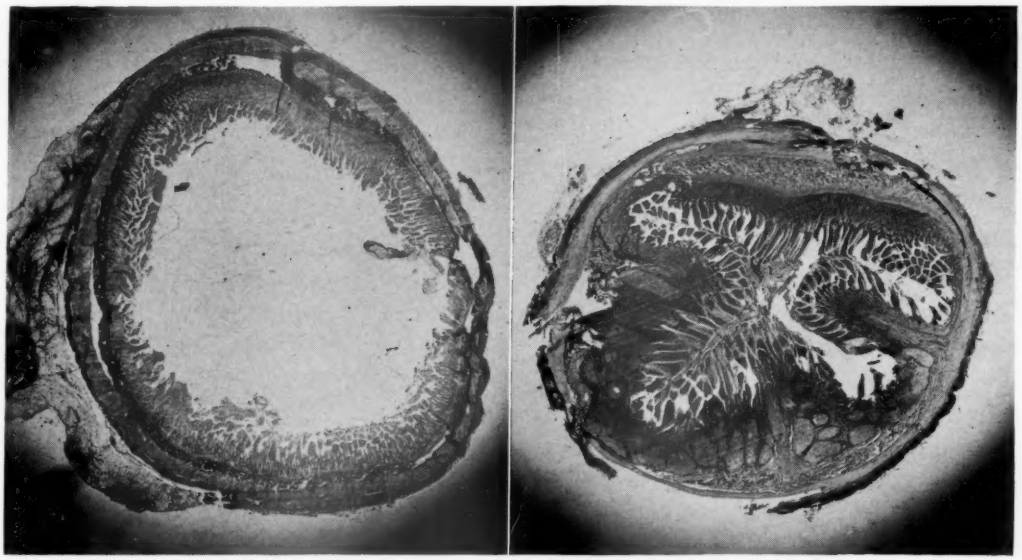

Fig. 2.—Photomicrographs of the same magnification showing control cross section of terminal ileum (left) as compared to cross section of terminal ileum (right) isolated from the fecal stream and into which had been injected finely divided sand. These sections were taken from the terminal ileum of the same dog within six inches of each other at the time of sacrificing the animal. Note the thickening of the bowel wall, the diminished lumen, and the submucous lymphoid hyperplasia in the section on the right as compared with the thickness of the wall, the size of the lumen, and the condition of the submucosa, respectively, in the control section on the left.

Fig. 3.—Photomicrograph showing lymphoid hyperplasia of the submucosa of the terminal ileum isolated from the fecal stream by a Thiry fistula and into the lumen of which had been injected a suspension of finely divided sand at the time of the operation. This lymphoid hyperplasia of the submucosa is considered by Hadfield[8] to be the primary lesion in regional enteritis.

were sacrificed by an intracardiac injection of nembutal at 22, 71, and 98 days after operation. The dogs which died within 8 days following injection of the talc suspension died of a plastic peritonitis. There was no evidence of leakage at the anastomotic site in any case, but the abdominal viscera were covered with a thick, sticky, whitish exudate. The dogs which survived and were sacrificed exhibited the same gross and microscopic picture as the animals injected with sand except that the serosal surfaces of the abdominal viscera were more granular in appearance and adhesions were more numerous in the talc-treated animals. Detailed summary of pathologic changes will be given later.

Into the blind loop of the terminal ileum and cecum of one dog was injected a solution of quinine sulfate (0.33 Gm. in 10 c.c.). The dog was sacrificed three weeks later. No significant pathologic change was found.

Four hours before sacrificing two dogs similarly operated upon and treated, one with sand and one with talc, a mixture of corn oil and Nile blue was introduced into the stomach of one by means of a Levine tube, and a mixture of corn oil and sudan III in the other. This was done to determine if the mesenteric lymphatics could be visualized, and the presence of obstructed areas noted. In neither case was the dye absorbed in sufficient amount, however, to produce a good contrast between normal and abnormal areas.

The thirteen dogs receiving 10 Gm. sea sand and 10 Gm. No. 200 mesh sand in the daily ration developed a peculiar syndrome at the end of three weeks characterized by a generalized dermatitis, loss of hair, enlargement of the inguinal lymph nodes, and weakness. For about one week it seemed that they would die. They recovered, however, and by the seventh week appeared to be lively and well although they exhibited bald spots for weeks thereafter. The explanation for this result may lie in the speculation that acute lymphatic obstruction develops early, leading to difficulties in intestinal absorption. New lymph channels may open and the animal then recovers.

Gross changes are typified in the case history of Dog. 2. This dog was sacrificed after three weeks of sand feeding when it appeared to be quite ill. Plasma protein, hemoglobin, and hematocrit determinations were made before sacrificing the animal as was done at regular intervals for the other animals in this series. The figures were found to be 4.1 Gm. per cent protein, 13.75 Gm. hemoglobin, and 37.3 hematocrit, which are considerably below the values for normal dogs, except the value for hemoglobin. However, in most of the other dogs similarly treated hemoglobin also was found to be under normal. There was a noticeable amount of thin serous fluid in the peritoneal cavity. The bowel wall distal to the duodenum was thickened as compared with that of a normal animal of the same size sacrificed at the same time. The mucosal folds were erased, the mucosa was very friable, and excoriated, hemorrhagic areas appeared scattered throughout the bowel except in the duodenum, which appeared to be normal. The lumen of the bowel did not seem to be diminished in caliber.

Animals which were sacrificed after having been fed sand for periods longer than two or three months revealed an additional finding. At necropsy hard, small, whitish spots were seen on the surface of the liver. A microscopic section

of the liver revealed numerous small granulomas (Figs. 4 and 5). Thereafter tissue sections of the remaining dogs were taken from the liver, spleen, adrenals, and kidneys, in addition to sections from bowel and mesenteric lymph nodes.

Fig. 4.

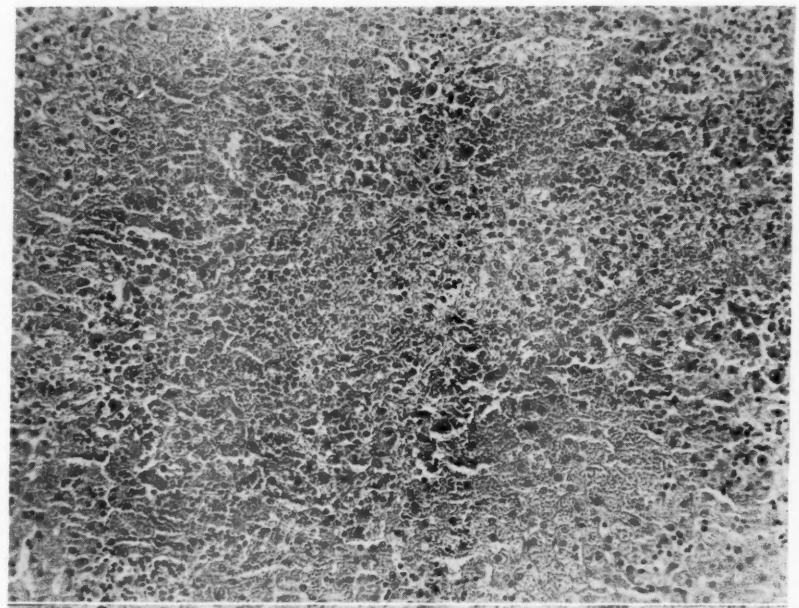

Fig. 5.

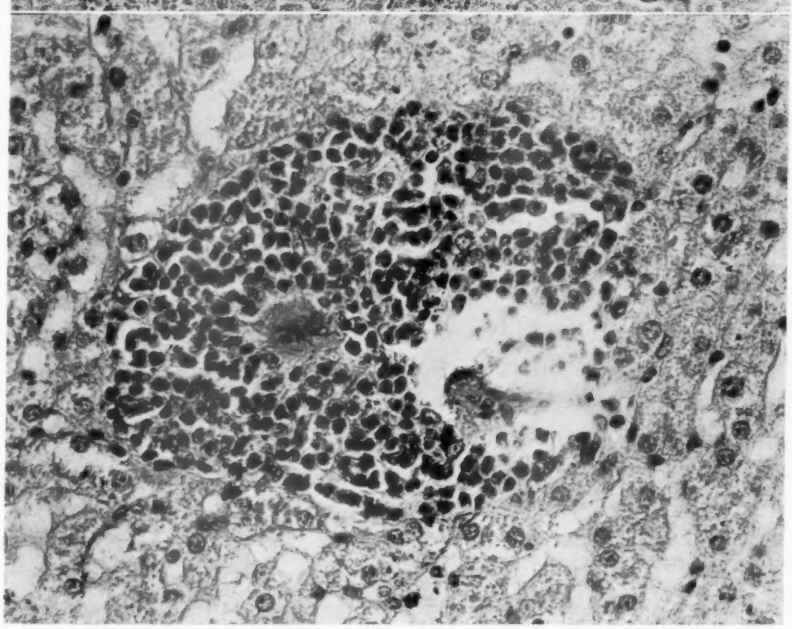

Fig. 4.—Photomicrograph of a section of the liver of a dog showing granulomatous lesions resulting from the absorption of finely divided sand from the gastrointestinal tract. This section, when viewed through the polarizing microscope, revealed numerous doubly refractile granules scattered throughout the lesion.

Fig. 5.—High-power magnification of granulomatous lesion in the liver of a dog in which absorption of finely divided sand from the gastrointestinal tract occurred. Note the whorl-like arrangement of the "chronic inflammatory cells" in the lesions and the presence of several "giant cells."

Dog 11, which was given sand for 165 days, died two days after receiving an injection of a broth culture of bacteria intravenously. Tissue changes did not differ from those of the other dogs in this series except that when the bowel was opened dark blood was found in the lumen.

A metabolism study on Dog 12 was carried out as described previously. It was noted that a considerable nitrogen imbalance was present by the third week which coincided with clinical signs of ill health appearing in the sand-fed dogs at the end of the third week. Several weeks before Dog 12 was sacrificed it received intravenous bacterial injections as described under Materials and Methods. After the third injection grossly bloody diarrhea was present.

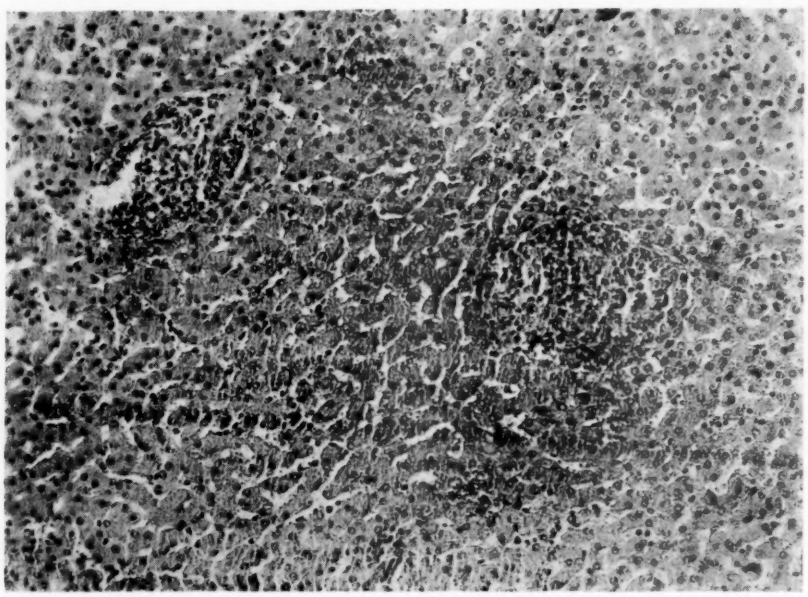

Fig. 6.—Photomicrograph of section of the liver of a dog which had been fed talc, U.S.P., in the daily ration. Note granulomatous lesions which are indistinguishable from those of the sand-treated animals.

Dog 13 was also placed on the metabolism study but was fed no sand for the first six weeks. During this six-week control period it was noted that the nitrogen retained or lost fluctuated greatly. There was a trend toward less nitrogen retention but not a negative balance during the following period when the animal was being sand fed.

Two healthy dogs (No. 14 and 15) were fed 10 Gm. talc, U.S.P., in their daily ration. This is the talc used in the operating room to powder surgical gloves. After six weeks the amount of talc in the diet of Dog 14 was increased to 30 Gm. daily. At fifty-two days from the beginning of the experiment the dog which had weighed 22 pounds at the beginning of the experiment weighed 15 pounds. The plasma proteins were 5.8 Gm. per cent; hematocrit, 24; and hemoglobin, 8 Gm. The dog was emaciated. It had lost nearly all its hair and there were ulcerating lesions in the skin over the entire body. The gross and microscopic observations including granulomatous lesions in the liver (Fig. 6) were indistinguishable from those of the sand-fed dogs in this series.

Dog 15 was fed 10 Gm. talc in the daily ration for eighteen days, after which the talc was discontinued. Four months later a bacterial mixture as

described previously was injected intravenously each week for three weeks. The dog developed bloody diarrhea after the first injection. One week after the last injection the dog was sacrificed. The gross and microscopic appearance was similar to that of sand-fed Dog 12. It is interesting to note that the duodenum in both the sand- and talc-fed animals remained normal and that the terminal ileum showed the greatest pathologic change (Fig. 7).

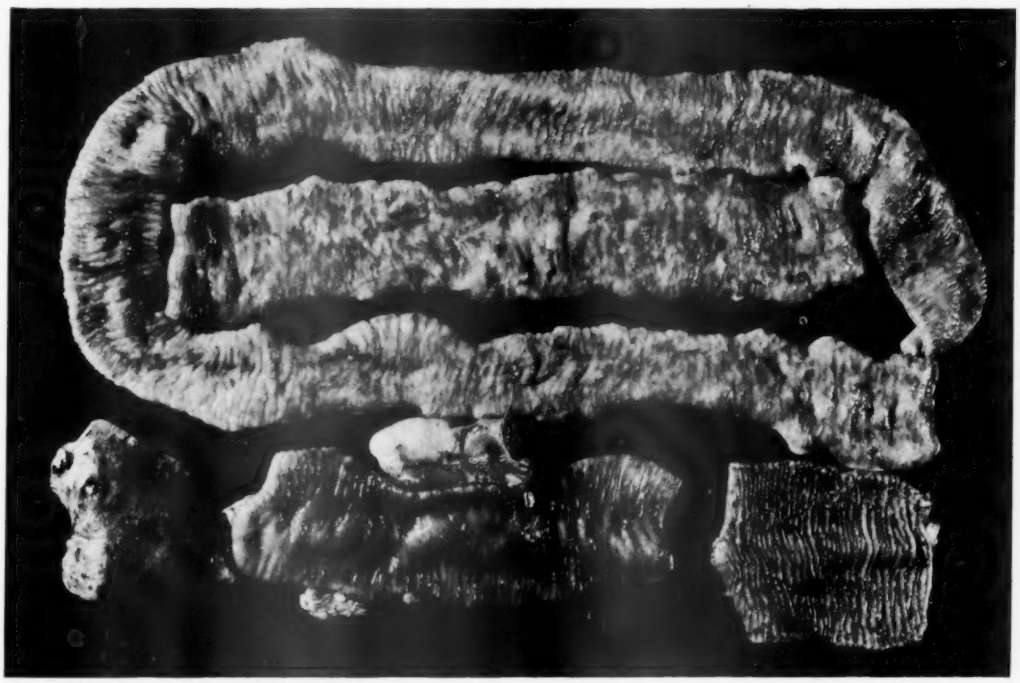

Fig. 7.—Photograph of opened intestinal tract of a dog sacrificed after three months of sand feeding and after receiving intravenous injections of laboratory strains of nonspecific bacteria. Gross blood was found in the intestinal lumen. Note the thickening and scarring of the bowel wall and the mucosal ulcerations especially in the encircled stretch of terminal ileum. A segment of duodenum is shown in the lower right. The duodenum appeared to be normal in all these animals. A piece of the liver appears in the lower left. Note granulomas on the surface.

Results of feeding finely divided sand to growing rats can be illustrated by comparing the growth curve of this group of rats with that of a control group (Fig. 8). By the end of three weeks there was a statistically significant retardation in the growth of the sand-fed rats as compared with the rats in the control group. This is in agreement with the slump in general health of dogs after feeding sand or talc for about three weeks.

## SUMMARY OF MICROSCOPIC TISSUE CHANGES

Of fifteen dogs whose tissues, including liver, lung, spleen, and kidney, as well as bowel and mesenteric lymph nodes, were studied, twelve showed a definite hyperplasia of lymphoid tissue of the small bowel as compared with that of normal dogs. Seven dogs showed microscopic granulomatous lesions of the liver. Thirteen dogs showed definite histologic evidence of hyperplasia of the regional mesenteric lymph nodes. This hyperplasia was a conspicuous gross finding.

The remaining pathologic observations were varied in nature from animal to animal and were infrequent. They included patchy bronchopneumonia in three dogs and patchy areas of infiltration with inflammatory cells in the kidneys of two dogs.

The lungs, spleens, kidneys, adrenals, and pancreases were histologically normal with the exceptions noted.

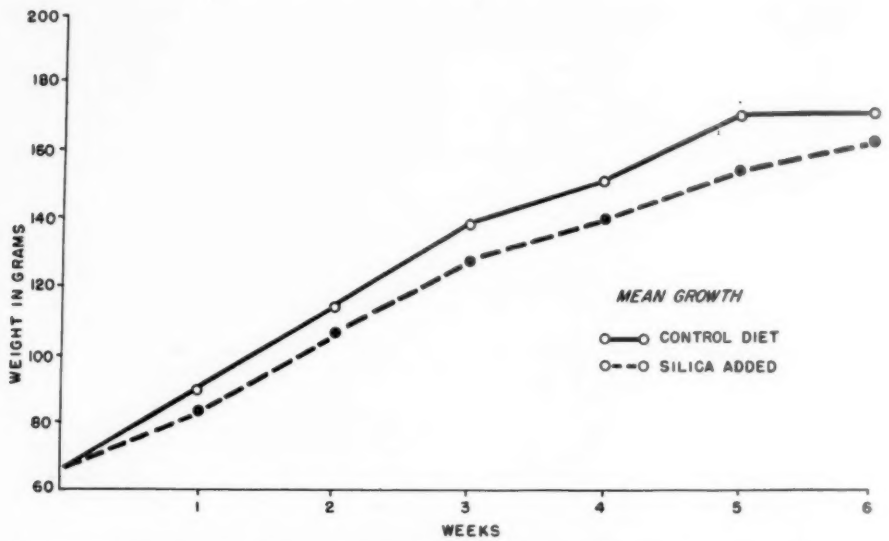


Fig. 8.—Graph showing growth curve of rats fed finely divided sand (broken line) in comparison with growth curve of control (solid line) group during a period covering six weeks. These growing animals were matched in age and weights at the beginning of the experiment and were fed the same basic diet except for 2½ per cent finely divided silica added to the diet of the group in which it produced retardation in growth (broken line).

The hyperplasia of the lymphoid tissue was so classified only when 50 per cent or more of the bowel circumference was involved and as compared with control sections wherein lymphoid tissue was relatively inconspicuous in amount. This hyperplasia consisted of a marked proliferation of lymphoid tissue in the submucosal layer of the intestinal wall. Frequently sections showed almost a continuous ring of lymphoid tissue encircling the bowel. This lymphoid tissue was composed in major part of huge lymph follicles containing large germinal centers consisting of large lymphocytes and surrounded by an inconspicuous stroma densely packed with small lymphocytes. Mitotic figures were frequently found in the germinal centers. No abnormal lymphocytic cells were noted. Sometimes the lymphoid follicles were "piled" three or four more "deep" producing a large eccentric mass in the submucosal tissue and displacing the mucosa inward. Such masses might be likened to a greatly hypertrophied Peyer's patch. Occasionally specimens showed a typical foreign body reaction. This was characterized by lymphocytic infiltration in the adventitial layer which contained a few foreign body giant cells.

Lymphoid hyperplasia in lymph nodes presented similar features, namely, increased numbers of follicles in the cortex containing huge germinal centers. In addition, there was often a conspicuous hyperplasia of the reticuloendothelial cells particularly in the medulla.

The granulomatous lesions found in seven of fifteen livers examined presented a somewhat varied picture. These lesions were of microscopic size and about 100 to 1000 micra in diameter. Such lesions were found sometimes within the liver lobule and sometimes at the portal triad regions; there was no particular type of distribution in relation to the anatomic unit. The number was also variable: As a rule two or three could be found in 1 sq. cm. of tissue; in one specimen about twenty lesions were found in that area of tissue. Serial or multiple sections were not made because of limitation of facilities.

The lesions were round to oval in contour and usually consisted of chronic inflammatory cells; the liver cells in the area occupied by the lesion apparently had been destroyed. One specimen showed lesions which consisted almost entirely of lymphocytes. Most of the others consisted of a mixture of cells with large mononuclear cells predominating, particularly in the central portion. Accompanying these were scattered lymphocytes, occasional neutrophils, and rarely eosinophils. In some lesions "epithelioid" cells centrally gave them the appearance of "pseudotubercles." In one specimen the lesions had an increased number of neutrophils and there was evidence of liquefaction necrosis in the central portions manifested by a granular acidophilic debris. In two specimens small giant cells appeared to be forming which consisted of a mass of acidophilic cytoplasm containing three or four oval nuclei centrally placed. Such cells were limited to one or two per lesion and were poorly formed.

Review of liver slides from thirty different dogs used for unrelated work revealed no comparable lesions. However, the majority of the granulomatous lesions of the livers of sand- or talc-treated animals under polarized light revealed large numbers of very fine doubly refractile granules distributed throughout the lesion.

## DISCUSSION

In 1942 Webb, Selle, and Thienes[21] studied the absorption, accumulation, and excretion of ingested silica from a chemical viewpoint. They fed four groups of rats a diet containing 1 per cent finely divided sand for ten months. The growth rates of the rats did not vary but they found that the ingested silica can be accumulated mainly in two organs, the liver and the spleen, supposedly being picked up from the blood where it circulates in colloidal form by the reticuloendothelial system. In the light of the newer concepts of the pathogenesis of silicosis, the pathogenic response depends not on the solubility and circulation in the blood in colloidal form but on the insolubility of the silica particle.[5] Webb, Selle, and Thienes studied the increase of silica in the organs mentioned by quantitative analysis. They did not report on tissue changes.

In 1945 Tebbens, Schulz, and Drinker,[19] reporting on the potency of silica particles of different size when injected intravenously into the ear veins of rabbits, found at the end of eighteen months that the livers of these animals were almost wholly replaced by fibrous tissue.

It appears to be quite well substantiated, therefore, that when finely divided silica is administered either intravenously or into the digestive tract it is deposited rather widely in the tissues. If this occurs in sufficient quantity or for a sufficient period of time, serious injury occurs to the organs in which the material is deposited.

This effect appears to be characteristic of quite a large number of finely divided materials possessing the asymmetrical crystalline form, for example, touramline (aluminum boron silicate), quartz or sand, wulfenite (lead molybdate), berlinite (aluminum orthophosphate), barium titanate, talcum powder, asbestos, and cholesterol. Among such irritating substances to which one is constantly exposed are tooth powders and pastes which contain a high percentage of very finely divided silica, as shown by Lanza[12] in a survey of industrial dusts constituting hazards. Beryllium phosphors (beryllium silicate) which are being used in the manufacture of fluorescent light bulbs constitute another new granuloma-producing hazard.[13]

*A Theory for the Pathogenesis of Nonspecific Enteritis.*—The germ theory for regional enteritis and perhaps for ulcerative colitis seems to be inadequate. Perhaps the patient's concept, that "It was something I ate," is the more likely explanation. This work was undertaken with that point of view. It was only recently, however, that a possible explanation could be offered. In order to understand this proposed explanation one must be familiar with the concept of piezoelectricity[3] and the newer concepts as to the pathogenesis of silicosis.[5]

Certain crystals such as quartz crystals have an asymmetrical arrangement of the atoms in the molecule. This asymmetrical arrangement gives such crystals the property of piezoelectricity. For example, if such crystal is placed under stress by applying pressure to it or by subjecting it to a certain vibratory frequency it will develop an electric charge on its surface. If such crystal is introduced into the tissues anywhere in the body a protective, cellular, proliferative reaction takes place, that is, a granuloma results. If such crystal is insoluble it remains in the tissues for the life of the organism causing progressive fibrosis. The same substance which at one time exists as an asymmetrical crystal may exist in a different form. For instance, quartz occurs as an asymmetrical crystalline material possessing the property of piezoelectricity but may exist as fused quartz or ground glass of the same particle size without possessing this property. Lanza[12] found in a preliminary survey of dusts that twenty-eight nonreactive silicates were in the symmetric class whereas the six reactive dusts, that is, those which produced silicosis possessed the asymmetric arrangement. Talc, asbestos, and other siliceous dusts which are occasionally reactive are capable of becoming asymmetric under reproducible conditions.[6] Diatomaceous earth is biologically inactive but after calcining at high temperatures a diffraction pattern of cristobalite arrangement appears and the "new" dust develops a pathogenicity in keeping with its new crystalline structure.[7] It was purely by accident that it was found that aluminum phosphate became crystalline in a quartz class when heated for purposes of sterilization. This substance also produced granulomas when injected into the peritoneal cavity of rats.[6] Quartz, the phospholipid capsule of the tubercle bacillus and cholesterol have been shown to exert a biologic influence which is both interchangeable and "symbiotically" additive when equal distribution is effected in similar tissue sites. This observation alone suggests a common mechanistic relationship among these substances.[6]

The question arises as to how talcum powder can have the effect of causing granulomas when introduced into the body either at surgery by way of the powdered gloves of the surgeon or as in the experiments reported here in which

talc was introduced into the gastrointestinal tract. It is felt by a group of investigators who are studying the problem[6] that about 4 per cent of talc, U.S.P., which is described in the United States Pharmacopeia as being composed of "a native hydrous magnesium silicate, sometimes containing a small proportion of aluminum silicate" is crystalline material of the quartz class.

*Particle Size.*—It has been known for a long time that particle size is a factor in the production of silicosis and that the smaller the particle the more potent it is. It is thought that in order to produce silicosis the particles must be 10 micra or less. Larger particles are probably expelled. The same general considerations probably hold for the material in the gastrointestinal tract. If a sample of No. 200 mesh sand is studied for particle size all gradations will be found from particles 1 micron in length or diameter to particles 100 micra in length. The largest particles in a sample of No. 400 mesh sand are about 60 micra in diameter or length. Using a rod mill one can grind particles to any desired size.

*Regional Enteritis—A Clinical or a Pathologic Entity.*—Most pathologists feel that although regional enteritis is a clinical entity, it is not a pathologic entity. For resected specimens of bowel taken from cases of regional enteritis they therefore report "chronic inflammation" or some similar diagnosis. A notable exception is Hadfield.[8] He felt that the submucous lymphoid hyperplasia which occurs in regional enteritis is the most important single pathologic feature. It is noted that most of the tissues examined in the course of this work presented that feature (Fig. 3). The similarity between microscopic sections taken from these tissues and those of human cases of regional enteritis is striking.

*Talcum Powder Deaths.*—The high percentage of deaths occurring in the series of dogs in which talcum powder was placed into isolated loops of intestines is inexplicable except that perhaps these deaths may have some explanation similar to that which occurred in Vorwald's remarkable experiment.[20] He injected a very finely divided biologically active dust into the heart of a guinea pig. A "quick death" within a matter of minutes resulted. The death mechanism is clinically and pathologically indistinguishable from the "protein" death in guinea pigs which have been sensitized and shocked anaphylactically. This death reaction does not occur when benign dusts are similarly injected or when aluminum hydroxide is added to the active dust suspension.

*Factor of Infection.*—Intravenous bacterial injections were given to three dogs which had been fed either sand or talcum powder. Bloody diarrhea resulted in all three dogs. Other investigators who have injected similar bacterial cultures into normal dogs observed no such effect.[14, 17] However, when lymphatic obstruction was produced by injecting sclerosing substances into the lymphatics of the mesentery first and when this was followed later by bacterial injections, bloody diarrhea resulted and cicatrization was more pronounced.[14, 17] From these data it may be deduced that although injection of bacteria into normal animals produces no apparent ill effects, it will inflict a localized infection in certain diseased areas, namely, the edematous and inflamed wall of the ileum. It is easily possible that part of the inflammation in ulcerative colitis and regional enteritis develops secondarily in a similar manner.

## SUMMARY AND CONCLUSIONS

1. Finely divided sand and talcum powder when placed into the gastrointestinal tract can be absorbed to the detriment of the animal.

2. Pathologic changes similar to those of regional enteritis occur when finely divided sand or talc is present in the gastrointestinal tract in sufficient quantity and for a sufficient length of time.

3. Systemic effects such as granulomatous lesions in the liver can be produced by the administration of finely divided sand or talc.

4. Talc seems to be more pathogenic than finely divided sand.

5. A theory as to the pathogenesis of regional enteritis is presented which ascribes the pathologic process to the presence of ingested material having the property of piezoelectricity and relegates the factor of bacterial invasion of the tissues to a place of secondary importance. We do not contend that the particular agents used in these experiments are the causative agents in regional enteritis, but that foreign material of this type could readily be etiologic factors.

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# PULMONARY DECORTICATION FOR FIBRINOFIBROTHORAX AND EMPYEMA IN CHILDREN

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THE empirical therapy of febrile conditions in children with sulfonamide compounds and penicillin has greatly reduced the severity of undiagnosed pulmonary infections and has also markedly decreased the incidence of associated infections of the pleural space. Adequate treatment of recognized acute postpneumonic empyema by the systemic and intrapleural use of the antibiotics has simplified the treatment of this condition and has made surgical intervention unnecessary in most cases. In twenty cases reported by Burnett and co-workers[1] the systemic and local use of penicillin brought about cure of various types of empyema in 80 per cent, only 20 per cent requiring surgical drainage.

In cases of unrecognized postpneumonic empyema, sulfonamide compounds and systemic penicillin used over a period of weeks will frequently bring about sterilization of the pleural space with return of the temperature and leucocytosis to normal without, however, a corresponding fall in the respiratory and pulse rates. Physical examination in such children will reveal a splinted hemithorax with markedly decreased or absent breath sounds on the involved side and frequently an associated scoliosis. X-ray examination will show various degrees of pulmonary collapse and pleural density due to the presence of a large amount of exudate and fibrin in various stages of organization. The semisolid nature of the fibrin and frequent loculation prevent aspiration of such fibrinofibrothorax even though large needles are used. The gradual organization of the fibrin and the formation of a dense fibrous layer adjacent and firmly adherent to the parietal and visceral pleural surfaces prevents expansion of the lungs and leads to contraction and splinting of the chest wall with the eventual formation of scoliosis. Drainage of such fibrinofibrothorax alone will not remove the fibrous plate and such procedure in itself will convert a sterile pleural space into an empyema with marked delay in the eventual expansion of the lung and obliteration of the pleural space. The operation of pulmonary decortication in children with pyogenic empyemas which have been converted into a fibrinofibrothorax by the use of antibiotics has in our experience brought about excellent results with minimal morbidity.

Thoracentesis and pleural instillation of antibiotics can be accomplished without difficulty in the early course of an empyema; however, because of early loculation and the presence of a large amount of fibrin with organization of the fibrin adjacent to the pleural surfaces into a fibrous layer, thoracentesis occasionally may become difficult or even impossible before the empyema space has been sterilized and the lung has been expanded. In such cases thoracotomy and tube drainage will fail to produce expansion of the lung at an early date. Pul-

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monary decortication even in the presence of infection in this type of empyema will bring about rapid expansion of the lung and obliteration of the pleural space.

Chronic empyema associated with a bronchial fistula has in the past been particularly difficult to treat satisfactorily. Drainage combined with suction to produce expansion of the lung is usually ineffectual and the instillation of antibiotics into the pleural space leads to flooding of the tracheobronchial tree. It is in such cases that decortication has proved of particular value. Expansion of the lung following this procedure leads both to obliteration of the pleural space and closure of the bronchial fistula.

No complete statistics are available to determine the present incidence of postpneumonic empyema in children, however, it appears to be quite low. In the past two years only ten children were referred to our service for the surgical treatment of empyema, conservative treatment having failed to bring about sterilization of the empyema and expansion of the lung with obliteration of the pleural space. Pulmonary decortication was used in all these children as the operation of choice with excellent results in every case.

A summary of the cases is presented in Table I. On reviewing the data it is apparent that the patients can be placed into three definite groups. The first group consists of seven children with an empyema which was converted into a sterile fibrinofibrothorax by the use of sulfonamide compounds and penicillin, the latter by intrapleural instillation in only two cases. In the second group, consisting of two patients with pyogenic empyema, treated with sulfonamide compounds and systemic and topical penicillin, sterilization of the empyema and expansion of the lung did not occur. One patient had a chronic empyema with a bronchial fistula. The case history of one patient of each group is now detailed.

## CASE REPORTS

CASE 2.—T. D., a white boy 2 years of age, was admitted to Children's Hispital on Oct. 4, 1946. One month prior to admission he had developed persistent fever associated with cough. The patient was treated with penicillin and sulfadiazine with some improvement; however, ten days after the onset of illness he began to have a daily fever. He was admitted to a general hospital where the penicillin and sulfadiazine therapy was continued, without improvement. A diagnosis of empyema was made and the patient transferred to Children's Hospital.

On physical examination the infant was found to be pale, emaciated, and had labored respiration. The temperature was 101.2° F., respirations were 56, and pulse was 100 per minute. The right side of the chest appeared larger than the left, with marked splinting of the costal movements. There was complete flatness to percussion throughout the right side of the chest and breath sounds were absent. The left side of the chest appeared hyperresonant. X-ray films showed marked density of the entire right thorax with a slight shift of the mediastinum to the left. The admission blood count was 24,700 white blood cells with a hemoglobin of 14.4 Gm. On Oct. 5, 1946, thoracentesis was performed, however, only a few drops of a clear fluid were obtained, which was sterile on culture.

The patient was placed on sulfadiazine by mouth in the usual dosage and given penicillin, 10,000 units intramuscularly, every three hours. Several attempts at thoracentesis in different parts of the right thorax revealed the presence of a few cubic centimeters of fluid, however, all cultures were negative. There was a gradual fall in the patient's temperature and on the tenth hospital day the temperature had returned to normal. The white blood cell count at this

TABLE I. SUMMARY OF CASES

| CASE, AGE (YR.) | ADMISSION DIAGNOSIS | DURATION OF SYMPTOMS PRIOR TO ADMISSION AND TYPE OF TREATMENT | BACTERIOLOGY | DURATION AND TYPE OF HOSPITAL TREATMENT PRIOR TO DECORTICATION | PREOPERATIVE DIAGNOSIS | LENGTH OF POSTOPERATIVE HOSPITALIZATION, END RESULTS |
|---|---|---|---|---|---|---|
| (1) N. R. 6 | Empyema, left; total | 4 Weeks; sulfadiazine, penicillin, systemic | Staph. aureus | 5 Days; systemic penicillin, thoracentesis and pleural penicillin twice | Empyema, loculated | 13 Days; lung expanded on discharge, cured |
| (2) T. D. 2 | Empyema, right; total | 4 Weeks; sulfadiazine, penicillin, systemic | No growth | 27 Days; systemic penicillin, thoracentesis unsuccessful, sulfadiazine | Fibrinofibrothorax | 13 Days; lung expanded on discharge, cured |
| (3) A. B. 2 | Empyema, left; total | 3 Weeks; sulfadiazine | Staph. aureus | 12 Days; systemic penicillin, thoracentesis and pleural penicillin three times | Empyema, loculated | 7 Days; lung expanded on discharge, cured |
| (4) R. P. 5 mo. | Empyema, left; loculated | 10 Days; no treatment | No growth | 16 Days; systemic penicillin sulfadiazine, thoracentesis unsuccessful | Fibrinofibrothorax | 8 Days; lung expanded on discharge, cured |
| (5) C. S. 4 | Empyema, left; total | 2 Days? no treatment | No growth | 17 Days; systemic penicillin sulfadiazine, thoracentesis and pleural penicillin four times | Fibrinofibrothorax | 9 Days; lung expanded on discharge, cured |
| (6) L. H. 5 | Empyema, left; loculated. Bronchopleural fistula | 4 Weeks; sulfadiazine, penicillin, systemic intercostal drainage | Staph. aureaus, Str. hemolyticus B. pyocyaneus | 7 Days; systemic penicillin aerosol penicillin and streptomycin | Empyema, loculated; bronchopleural fistula; cutaneous sinus | 10 Days; lung expanded on discharge, cured |
| (7) M. G. 9 | Empyema, right; loculated | 5 Days; sulfadiazine | No growth | 14 Days; systemic penicillin thoracentesis unsuccessful | Fibrinofibrothorax | 9 Days; lung expanded on discharge, cured |
| (8) L. P. 4 | Empyema, right; total | 3 Weeks; penicillin, systemic | No growth | 2 Days; systemic penicillin, thoracentesis unsuccessful | Fibrinofibrothorax | 9 Days; lung expanded on discharge, cured |
| (9) D. R. 9 mo. | Empyema, right; total | 8 Days; sulfadiazine | No growth | 15 Days; systemic penicillin, sulfadiazine, thoracentesis unsuccessful | Fibrinofibrothorax | 7 Days; lung expanded on discharge, cured |
| (10) T. K. 12 | Lobar pneumonia; empyema, right | 3 Days; no treatment | No growth | 19 Days; systemic penicillin, sulfadiazine, thoracentesis and pleural penicillin four times | Fibrinofibrothorax | 10 Days; lung expanded on discharge, cured |

time was 11,100 with a hemoglobin of 11.5 Gm. X-ray examination following bronchography at this time showed a 90 per cent collapse of the right lung with several small areas of decreased density in an otherwise dense right hemithorax suggestive of a loculated fibrinofibrothroax. There was dorsal scoliosis (Fig. 1). Since aspiration of fluid from the chest could not be accomplished, decortication was performed on Oct. 31, 1946, four weeks following admission. Intratracheal cyclopropane-oxygen anesthesia was used. A right posterolateral incision was used and a portion of the seventh rib resected. The parietal pleura was covered by a densely adherent membrane measuring approximately 6 mm. in thickness and the thorax was filled with a large amount of fibrin mixed with serosanguineous fluid and interspersed with strands of fibrous tissue between the parietal and visceral pleuras (Fig. 2). On removing the fibrin and fluid from the pleural space and breaking the firm adhesions, the visceral pleura was also found to be covered by a thick membrane. On increasing the intratracheal pressure no expansion of the lung occurred. Decortication was performed without difficulty, the visceral pleural fibrous plate measuring approximately 5 mm. in thickness. The parietal, diaphragmatic, and mediastinal pleural surfaces were stripped. On completion of the decortication increased intratracheal pressure produced complete expansion of the lung.

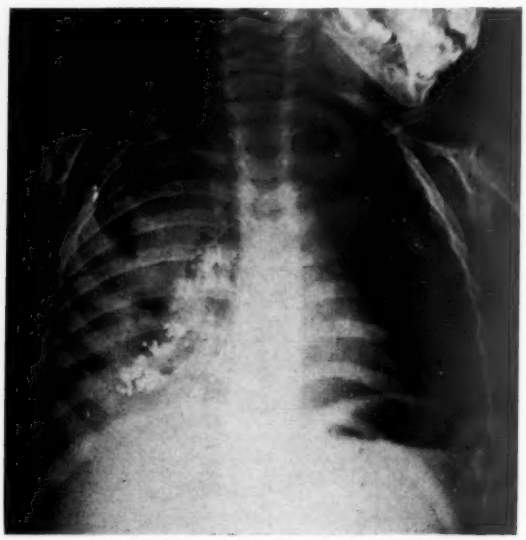

Fig. 1 (Case 2).—Preoperative film showing a total fibrinofibrothorax with 90 per cent collapse of the lung as demonstrated by bronchography.

Penicillin, 1,000 units in 5 c.c. of saline solution was injected into the pleural space and the thorax drained through an anterior intercostal No. 20 pezzar catheter which was connected to an underwater trap. Culture of the removed fibrin and fibrous tissue was negative for bacteria, and microscopic sections of these tissues revealed fibrin with organizing fibrous tissue containing numerous white blood cells, however, no organisms as such were seen. The patient was given 10,000 units of penicillin every three hours postoperatively, however, there was a temperature rise to 102.6° F., rectally on the first postoperative day with a gradual fall and return of the temperature to normal on the seventh postoperative day. An x-ray examination of the patient's chest forty-eight hours following surgery showed complete expansion of the lung. The pezzar catheter was removed following the instillation of another 100,000 units of penicillin into the thorax through the drain. The patient was allowed out of bed on the third postoperative day and was discharged on the twelfth postoperative day, x-ray films at the time showing complete expansion of the right lung. Roentgenogram taken six months postoperatively showed a regenerated seventh rib with normal lung fields and a clear costophrenic angle on the right (Fig. 3).

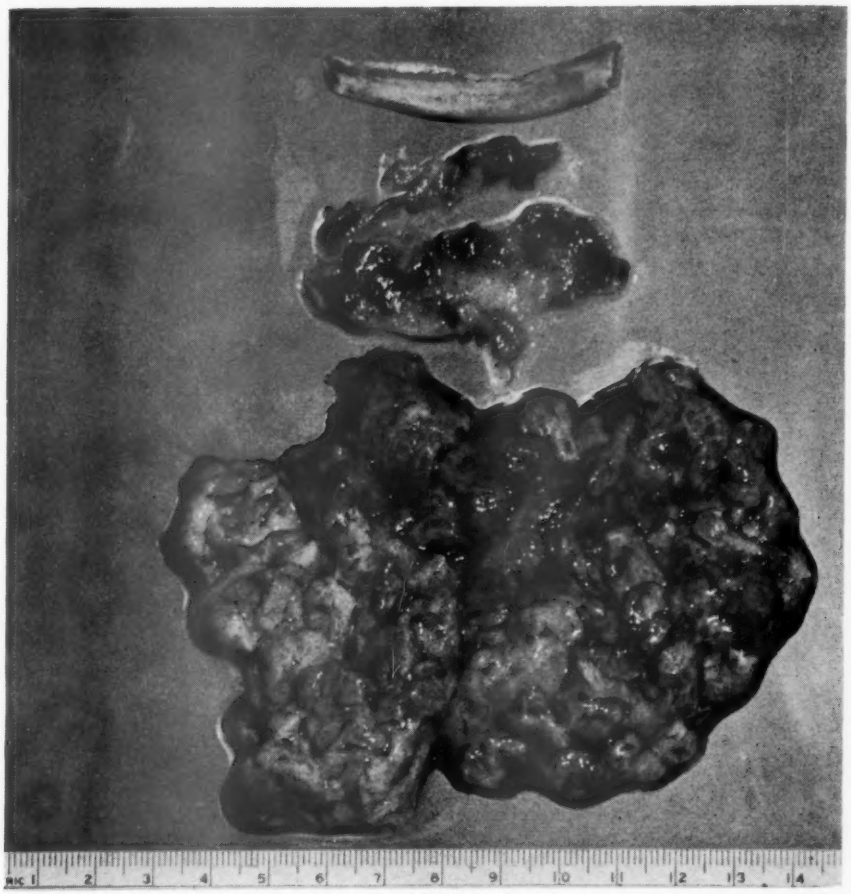

Fig. 2 (Case 2).—Portion of the resected seventh rib, the fibrous membrane, and large mass of fibrin removed during the thoracotomy.

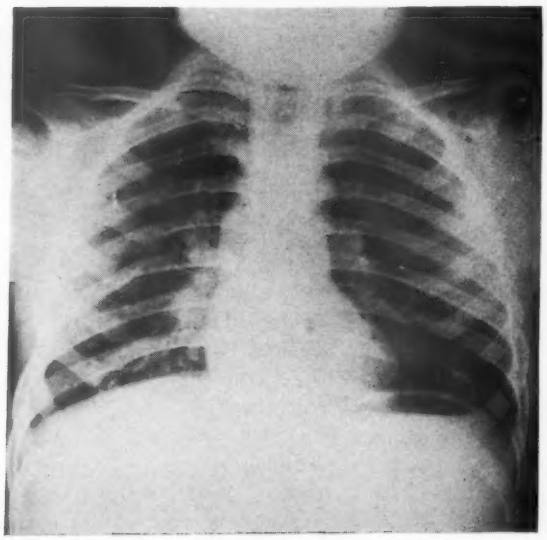

Fig. 3 (Case 2).—X-ray film taken six months postoperatively, showing a normal thorax. There is no scoliosis.

A postpneumonic empyema in this patient was converted into a sterile fibrinofibrothorax by the use of sulfadiazine and penicillin over a period of eight weeks. Thoracotomy with removal of a large amount of fibrin and pulmonary decortication permitted prompt re-expansion of the lung and complete obliteration of the pleural space.

CASE 3.—A. B., a 2-year-old white girl, was admitted to the hospital on March 23, 1947, with a history of having had an upper respiratory infection approximately three weeks prior to admission which was followed by pneumonia. The patient had been treated with sulfadiazine with some improvement; however, twenty-four hours prior to admission there had been marked increase in the patient's fever and she had developed marked shortness of breath.

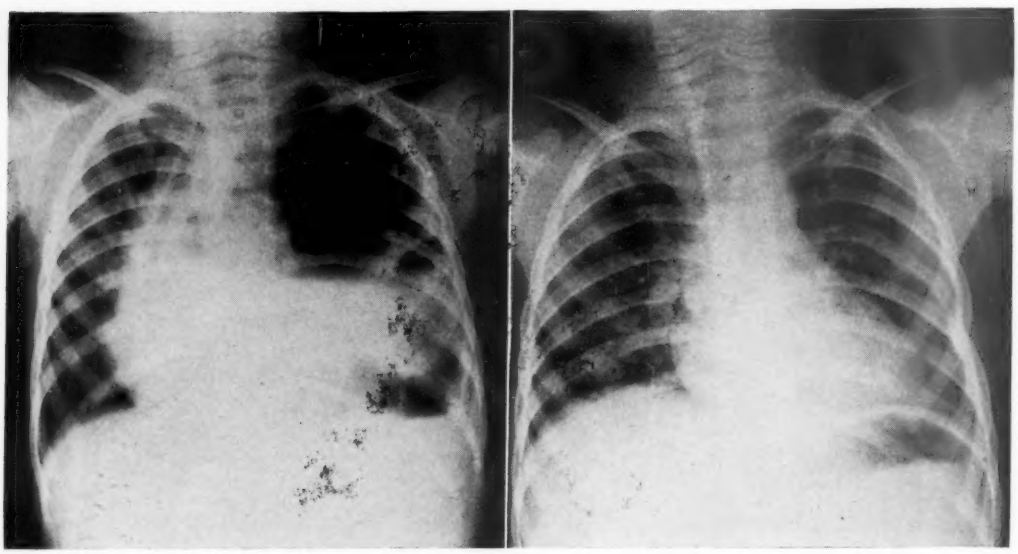

Fig. 4. Fig. 5.

Fig. 4 (Case 3).—X-ray film of April 1, 1947, showing a marked shift of the mediastinum to the right. There is complete collapse of the left lung with loculation at the base.

Fig. 5 (Case 3).—X-ray film taken seven months postoperatively. The mediastinum is in midline and the left costophrenic angle is clear.

On examination the baby was found to be quite pale and showed moderate dyspnea. The temperature was 102.6° F., with a pulse of 100 and respirations of 36 per minute. There was diminished expansion of the left side of the chest with increased basal dullness both anteriorly and posteriorly. Breath sounds were diminished over this area. There was a shift of the heart to the right. X-ray examination showed increased density below the fourth rib posteriorly with marked shift of the mediastinum to the right. The white blood count was 34,350 with a hemoglobin of 10.3 Gm. A diagnosis was made of left empyema and a thoracentesis was performed with removal of 125 c.c. of a cloudy yellow fluid, which on culture showed the presence of *staphylococcus aureus*. Penicillin, 50,000 units, and 10 c.c. of saline solution were introduced into the pleural space and the systematic administration of 10,000 units of penicillin every three hours continued. There was a slight drop in the patient's temperature following this procedure and thoracentesis was repeated two days later, at which time 180 c.c of clear straw-colored fluid was removed. Again 50,000 units of penicillin in 10 c.c. of saline solution were instilled into the pleural space. The fluid contained *Staph. aureaus*. A third thoracentesis was performed two days later, at which time 100 c.c. of a straw-colored clear fluid were removed, which contained fibrin particles. Again 50,000 units of penicillin were introduced into the pleural space. Culture of the fluid removed again showed the presence of *Staph. aureus*. Several repeated attempts at thoracentesis two days later failed to produce pus even though a large needle was used.

An x-ray taken on April 1, 1947 (Fig. 4) showed a marked shift of the mediastinum to the right with a left pneumothorax and fluid loculation in the left base. A needle was introduced into the left thorax in an attempt to decrease the tension pneumothorax. Air was allowed to escape; however, the patient's respiratory difficulties continued and aspiration of air did not return the mediastinum to the midline. On April 5, 1947, a left posterolateral thoracotomy was performed with resection of a portion of the sixth rib. The anesthesia was intratracheal cyclopropane-oxygen. When the pleural space was entered a considerable amount of fibrin deposits were found over both the parietal and visceral pleuras with a large amount in the lower portion of the thorax. A firmly adherent 2 mm. thick fibrous membrane covered the pleural surfaces. The fibrin was removed and decortication was performed without difficulty. Following this procedure there was complete expansion of the lung on increasing the intratracheal pressure. Penicillin, 100,000 units, in 10 c.c. of saline solution was placed into the pleural space and a No. 20 pezzar catheter was used in the sixth interspace anterior axillary line, which was connected to an underwater trap. On the day of the operation the patient's temperature was normal. It rose to 102.6° F., on the first, however, and returned to normal on the fifth postoperative day. The patient was discharged on the seventh postoperative day, x-ray films showing complete expansion of the left lung. Culture of the removed fibrin showed the presence of hemolytic *Staph. aureus*. X-ray films made seven months later revealed a normal thorax (Fig. 5).

A *Staph. aureus* empyema was treated with systemic and topical penicillin for twelve days without sterilization of the pleural infection. A tension pneumothorax could not be controlled by aspiration. Decortication resulted in prompt expansion of the lung.

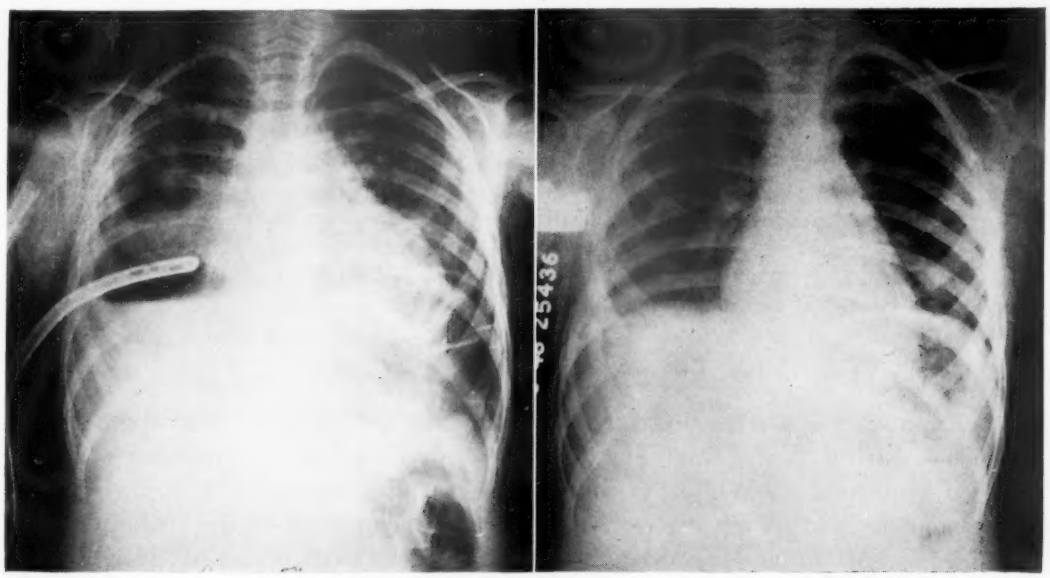

Fig. 6. Fig. 7.

Fig. 6 (Case 6).—Admission x-ray film showing loculated empyema with inadequate intercostal drainage tube.

Fig. 7 (Case 6).—X-ray film of April 6, 1948. There is no scoliosis.

CASE 6.—L. H., a 5-year-old white girl, was admitted to the hospital on Nov. 25, 1947, with a diagnosis of a right chronic empyema associated with a bronchopleural-cutaneous fistula. Approximately four weeks before admission this girl developed a cough with general malaise and fever, which was diagnosed as bronchopneumonia. The patient was admitted to a local hospital when she failed to respond to sulfadiazine. A roentgenogram taken on admission showed a fluid level in the right thorax and on thoracentesis *Staph. aureus* were found. In-

tercostal drainage was instituted; however, the patient's temperature continued to be high and there was no improvement in her condition. Penicillin and sulfadiazine were used in the usual amount.

On admission to Children's Hospital the patient had a temperature of 102° F., with respirations of 30 and a pulse of 90 per minute. There was complete splinting of the right thorax and on percussion dullness was present over the right side of the chest with diminished breath sounds. X-ray examination showed an irregular loculated empyema space on the right with thickened parietal pleura (Fig. 6). The white blood count was 11,150 and the hemoglobin 10.4 Gm.

Methylene blue instilled into the empyema space through the No. 14 French catheter was promptly coughed up, confirming the diagnosis of a bronchopleural fistula. Culture of the pus obtained from the cutaneous sinus revealed the presence of hemolytic streptococci, hemolytic *Staph. aureus* and *Bacillus pyocyaneus.* The patient was placed on aerosol penicillin and streptomycin together with systemic penicillin, 10,000 units every three hours. A transfusion of 200 c.c. of whole blood was given and under this management the patient's temperature returned to normal in one week. On Dec. 2, 1947, a right posterolateral thoracotomy with decortication was performed with resection of a portion of the seventh rib.

The pleural surfaces were covered with a firm, fibrous membrane measuring 3 mm. in thickness. A bronchial fistula was found on the anterior surface of the upper lobe. Decortication of all pleural surfaces was accomplished without difficulty. No attempt was made to close the bronchial fistula, since increased intratracheal pressure produced excellent expansion of the right lung.

An anterior intercostal No. 28 French pezzar drain was used for water-seal suction. The patient's temperature rose to 101° F., postoperatively, however, it returned to normal on the third postoperative day. X-ray examination of the chest on the second postoperative day revealed complete expansion of the lung, at which time the intercostal drainage tube was removed following instillation of 100,000 units of penicillin into the pleural space. The patient was discharged on the tenth postoperative day with complete re-expansion of the lung. The removed cortex on microscopic examination showed fibrous tissue with evidence of acute and chronic inflammatory reaction. Numerous bacteria were seen in the sections. X-ray films of April 6, 1948, revealed complete re-expansion of the lung. There was no scoliosis (Fig. 7).

A 5-year-old girl with a postpneumonic unrecognized and inadequately treated empyema developed a bronchopleural fistula. Inadequate intercostal drainage failed to produce expansion of the lung. Pulmonary decortication resulted in expansion of the lung with closure of the bronchopleural fistula and obliteration of the pleural space.

## DISCUSSION

Pulmonary decortication for organized and also infected hemothorax came into use during World War II. This method for rapid re-expansion of a collapsed lung held down by a fibrous plate was later successfully applied in the treatment of postpneumonic empyema. The development of the principles and techniques of pulmonary decortication has been well reviewed by Burford, Parker, and Samson,[2, 3, 4] Sanger,[5] and Langston and Tuttle.[6] These authors have discussed the pathologic changes occurring in the pleural space with the deposition and organization of the fibrin found both in hemothorax and empyema. We have essentially followed the surgical technique advocated by these surgeons. Several points, however, need re-emphasizing and minor variations have been used in the treatment of fibrinofibrothorax and empyemas in children.

Since the diagnosis of empyema was made in the majority of these children at a late date, the average time elapsing between the onset of symptoms and the surgical treatment of the condition was thirty days. During this time these

children had received both penicillin and also sulfonamide compounds and it is probably due to the latter that the average hemoglobin and red blood count was rather low. For this reason a preoperative blood transfusion was given whenever indicated and also a transfusion was given during the operation for the replacement of blood loss which was considerable in some of these infants. The sulfonamides were discontinued as soon as the patients entered our service; however, the penicillin was continued preoperatively in the usual dosage, and during the operation 50,000 units of penicillin were given with the infusion.

The anesthesia in all the patients was intratracheal cyclopropane-oxygen with ether induction. Adequate aspiration of the tracheobronchial tree could be accomplished without difficulty throughout the operation and the intratracheal pressure could be increased during the operation to test the adequacy of the decortication and also to determine possible tears in the visceral pleura. No pre- or postoperative narcotics were used in any of these children.

The approach was by the usual posterolateral incision with an intercostal incision in the younger babies and resection of a portion of the rib in the older individuals. In the last four patients an intercostal incision was used with section of the adjacent two ribs and consequent pegging. Adequate exposure was obtained. It was found easiest to begin the decortication by entering the posterior gutter through the fibrous plate and exposing the uninvolved portion of the pleural space in the hilar region. By applying gentle traction on the edge of the fibrous plate the blunt end of the knife handle, finger, or gauze was used to develop the cleavage plane. Bleeding from the pleural surfaces was controlled on application of hot saline packs in a relatively short time. Small tears in the visceral pleura occurred occasionally, however, they were not sutured, sealing spontaneously in a few minutes. The visceral as well as parietal pleuras were decorticated following the removal of all fibrin and breaking up of loculations. The diaphragmatic fibrous plate was also removed and decortication was considered adequate when on increasing the intratracheal pressure there occurred complete expansion of the lung.

Following the instillation of 100,000 units of penicillin in 10 c.c. of saline solution into the pleural space, the thorax was carefully closed in layers with a small pezzar catheter placed in the incision at the level of the anterior axillary line and connected to a water seal. The systemic penicillin was continued postoperatively for an average of five days. The catheter was removed in forty-eight hours, at which time x-ray examinations showed expansion of the lung and absence of blood and serosaguineous fluid in the pleural space. Penicillin, 100,000 units, was again placed into the pleural space just prior to the removal of the catheter.

A marked scoliosis which had developed in one patient required physiotherapy for correction; however, no such methods were used in the other children, all of whom had developed a scoliosis prior to decortication. Subsequent examination showed no residual spinal deformity.

In the seven children with the sterile fibrinofibrothorax, sections of the tissues removed at operation showed exudate and fibrin in various stages of organi-

zation. The layer next to the pleura showed small blood vessels and fibrous tissue. Culture of this material was negative for bacteria and no organisms were seen in the microscopic section. In the three children with the empyema still present at the time of decortication, bacteria were demonstrated both in microscopic sections and on culture of material removed during the operation.

## SUMMARY

In seven children a postpneumonic empyema was converted into a sterile fibrinofibrothorax following an average period of thirty days treatment with sulfonamide compounds and penicillin systemically. In only two of these children was penicillin used intrapleurally. Pulmonary decortication in these patients resulted in rapid and complete expansion of the lung and obliteration of the pleural space. The average postoperative hospitalization of these seven patients was nine days.

In two children with postpneumonic empyema, treatment with sulfonamide compounds and both systemic and topical penicillin failed to sterilize the empyema space and bring about expansion of the lung. Following pulmonary decortication there was immediate complete expansion of the lung.

In one patient with a chronic empyema and bronchopleural-cutaneous fistula, pulmonary decortication resulted in complete re-expansion of the lung, closure of the bronchopleural fistula, and obliteration of the pleural space.

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# FURTHER DEVELOPMENT OF THE GASTRIC BALLOON TO FACILITATE INTESTINAL INTUBATION

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SINCE the introduction of the gastric balloon technique,[1] designed to force a long intestinal tube across the stomach from the fundus to the pylorus, some further modifications have been made.

Wyndham[2] (1946) first remarked on the flattening of the stomach which occurred in the presence of marked bowel distention and noted the difficulty in getting Miller-Abbott tubes to point toward the pylorus. During the clinical evaluation of a design of long intestinal tube[3] which seemed to show more promise of bringing about rapid decompression of distended bowel, the observation of Wyndham was confirmed. Massive air injection made possible by the design of tube was found in most cases to overcome the problem of the flattened stomach and to have little if any deleterious effect on the patient.[4]

However, there remained some cases in which, for some reason, the stomach could not be inflated with gas. These cases were found to be comparatively rare and were usually associated with a very tense abdominal wall in the presence of small bowel distention. They may occur postoperatively or from primary small bowel distention and usually the distention is either of long standing or has arisen acutely in the presence of good tonus of the abdominal musculature. The rarer cases in this group are concerned, in the experience so far gained, with the inability of the stomach wall to stretch and with the integrity of the esophageal sphincter. One case has been encountered in which it was found impossible to distend the stomach with air under fluoroscopic visualization. A diagnosis of diffuse carcinomatosis, the so-called "leather-bottle stomach" was made and confirmed at celiotomy. Two additional cases in this group of rarer cases have been observed in which the patients, although not sufficiently distended, as far as could be judged, to require a gastric balloon, were unable to hold injected air in the stomach. Injection of air revealed fluoroscopically some slight increase in size of the fundal area of the stomach but a passage to the pylorus could not be opened because of almost immediate eructation of the injected air.

During an attempted gastric balloon intubation on a severe bowel distention of postoperative origin, it was found that, when the balloon was inflated to 600 c.c. the patient could not tolerate any further increase in intra-abdominal pressure due to the pain arising from the operative site. Since at least 1000 c.c. had been found to be necessary in order to deliver the tip of the tube to the pylorus, the attempt was abandoned. Thus, although it had been found that

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cases unassociated with recent operation could tolerate the extreme distention of the gastric balloon temporarily, the method was useless in postoperative cases.

It was decided to try to reduce the volume of balloon necessary to achieve the transport of the tube tip across the stomach. Three types of apparatus* were developed as shown in Fig. 1.

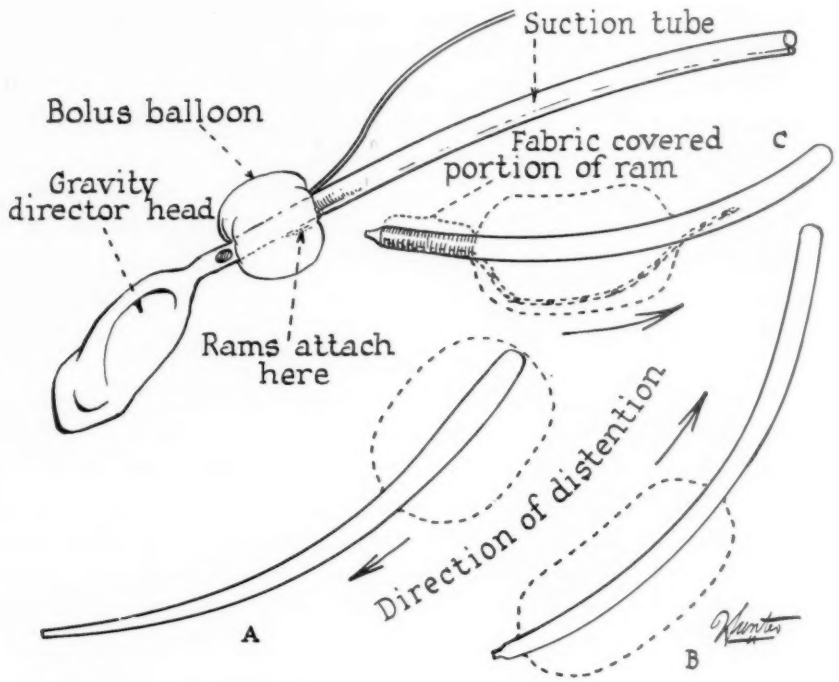


Fig. 1.—The author's standard tense balloon-bolus, terminal supported twin-holed long intestinal tube with the gravity director head introduced in 1944. In addition, the attachment of the "gastric ram" can be seen, together with the plastic tube placed therein. The tapered balloon *A* inflates first at the free end and then toward the point of attachment. The parallel balloons, *B* and *C*, inflate as indicated. A pneumatic probe, formed by inflation under pressure of the fabric-covered portion of the ram, can be seen at *C*.

## DESCRIPTION OF APPARATUS

Fig. 1 shows the standard tube in use at the institution of origin of this communication. Also shown are three types of attachable balloons, attached as near the tube tip as possible. These balloons represent a gradual development of the apparatus in the light of clinical experience. I have called them "gastric rams."

The action of these rams is fundamentally different from that of the gastric balloon. The gastric balloon, a full-length blunt-ended condom, requires only a relatively small inflation pressure and takes a large volume of air before the stomach walls are fully stretched. The pyloric region is thus drawn onto the tip of the tube in a manner somewhat analogous to drawing the finger of a tight glove onto the finger. On the other hand the ram, upon inflation, extends con-

*Made possible through the courtesy of the American Anode Company, Akron, Ohio, which supplied the necessary materials.

siderably in length and only minimally in diameter, similar to a "sausage" balloon. Ram *A* shown in Fig. 1 was a conically shaped balloon having a maximum diameter of 9 mm. and a minimum diameter of 4 mm. Its length was 12.5 cm. The wall thickness was approximately 5 to 8 thousandths of an inch. When fully inflated the internal pressure was 11 cm. of mercury, it had a minimum diameter of 2.5 cm. and a maximum of 5 cm. The length when inflated was 50 cm. Inflation started at the maximum diameter, namely at the free end distal to the point of attachment to the intestinal tube, and proceeded toward the attached end as indicated. Thus, when inflated the blind end came to lie in the fundus of the stomach and, as inflation proceeded, the tip of the tube was drawn to the pylorus (Fig. 2).

Clinical trial of this type of ram revealed a tendency for the balloon to burst (Case 2). The reason was not entirely clear but was thought to be due to kinking of the ram in the stomach. Accordingly, it was thought that if a ram could be made which inflated from the fixed point on the tube toward the free end, this obstacle would be eliminated. It was considered technically very difficult to achieve this end until a chance observation was made that if a long parallel-walled balloon was caused to begin to inflate at a given point after fabrication, it would always start to inflate at this point thereafter. Thus, the Ram *B* shown in Fig. 1 came into being. It consisted of a parallel-walled balloon of 6 mm. diameter and 14 cm. in length. The wall thickness was 20 to 25 thousandths of an inch. After fabrication it was "trained" to blow up from the point of attachment toward the free end, as indicated. This ram required a considerably higher pressure to inflate it, and a bicycle type inflation pump was used for the purpose. When fully inflated a rigid penis-like structure was produced, having 3.5 cm. diameter and 60 cm. length. The pressure within the ram was 35 cm. of mercury.

The action of this ram was visualized fluoroscopically in Case 2 (Fig. 4). The tip of the tube was seen to progress from the fundus to the pylorus as inflation proceeded.

The development of Rams *A* and *B* represents a reduction of volume of balloon in the stomach with an increase in operating pressure, resulting in a more rigid balloon.

A further improvement is shown at *C* of Fig. 1. This development was deemed desirable since the type *B* ram could deliver the tip of the tube only to the pyloric region and perhaps just beyond. A rigid extension to the type *B* ram was conceived and fabricated in one piece by incorporating some fabric in the wall, as shown. This design is completely flexible and easily introduced through the nose. Upon inflation a pneumatic probe, 3.5 cm. in length and 1 cm. in diameter, is formed between the point of attachment of the ram and the point of progressive inflation toward the free end. In this way it was thought the ram would force the tip of the tube well beyond the pyloric region and into the second part of the duodenum. This was confirmed in practice (Case 3). Fur-

ther, it was considered that in the less severe degrees of distention, it might be possible to push the tube tip into the duodenum by manipulation through the anterior abdominal wall (Fig. 6), at least in thin subjects.

It has been found that there is a distinct tendency when carrying out gastric balloon manipulations for the gravity director head to flop back and get tangled with separate inflation tubes. For this reason it is desirable to avoid, where possible, multiple separate inflation tubes, even on experimental tubes used for development. Therefore, in order to reduce the number of separate inflation tubes to unity, an Honor-Smathers double-lumen tube[5] was modified according to the principles of design so far found the most satisfactory[4] so that only the gastric rams required separate inflation tubes. Where multiple separate tubes have to be used, pending the availability of multiple-lumen tubes, they should be bound onto the suction tube carefully for the first 24 inches. The elimination of the gravity director head altogether is probably not a good plan, since by its agency swallowing is greatly facilitated in very ill patients. Also, the gravity director head probably has important functions once the pylorus has been reached and thereafter.

In order to insure complete deflation of the gastric ram, a small perforated plastic tube is placed inside. This prevents air from getting trapped during deflation by the formation of kinks.

## CLINICAL CASES

CASE 1. (No. 799968).—A well-developed white man of 62 years was found to be extremely distended five days following a combined abdominoperineal resection for carcinoma of the rectum. Considerable resistance of the abdominal wall was encountered by the palpating fingers. Bowel sounds were weak and very infrequent. Intubation was attempted by the standard technique of massive air injection, and it was not found possible to deliver the gravity director head to the pylorus. Five hours of right-side lying were allowed, after which the gravity director head was found not to have moved out of the fundus of the stomach. In other words, it was held under the diaphragm on the left side by the compressed stomach walls and had not been passed to the pylorus by activity of the stomach walls. After this trial of the standard technique it was deemed advisable to use some mechanism for forcing the tip of the tube to the pylorus. Accordingly, the tube (Fig. 1, *A*) was passed in the usual way into the nostril without difficulty. On arrival in the fundus, air was injected into the stomach and it was once again found impossible to open a passage to the pylorus. A further unsuccessful attempt was made to get the gravity director head across the stomach by positioning the patient and by further inflation. More of the tube was swallowed in order to be sure of getting the ram into the fundus before inflation. This caused the tube to coil in the fundus of the stomach. The ram was then inflated with air to half-volume approximately, and the tube was pulled back to uncoil. It was then allowed to pass across the stomach as further inflation was occurring. The patient was positioned nearly prone and with the table 45 degrees, feet down. This delivered the tube into the pyloric region (Fig. 2) and perhaps into the duodenal bulb. At this stage the patient was rolled onto his back and the table tilted nearly vertical with the feet down.

Deep waves of gastric peristalsis passing over the inflated balloon were observed at this point. An attempt was made to force the tube still further by inflating the ram still more. The result was a dull thud within the patient, followed by eructation of gas, and the gravity director head was seen to move into the second part of the duodenum (Fig. 3). By the next morning the tube had passed into the jejunum and the following day the bowel was nearly decompressed.

The tube was removed in error at this point and further distention occurred. Shortly afterward a standard tube without a ram was passed easily to the pylorus with massive air injection. It passed overnight into the duodenum. The degree of distention was considerably less than at the primary attempt. Decompression was accomplished and after eight days the tube was removed. The patient made an uneventful recovery from this point.

Fig. 2.

Fig. 3.

Fig. 2.—A radiograph of the first case described in the text. This demonstrates the gravity director head delivered to the pyloric region as described. The conical-shaped "gastric ram" (Fig. 1, *A*) can be seen filling the stomach, and the tube entering the fundus obliquely and curving around to the right side of the patient. The gravity director head was visualized fluoroscopically in the first part of the duodenum in the lateral position.

Fig. 3.—This radiograph was taken a few minutes after Fig. 2, after the "gastric ram" had burst without harm to the patient. The bursting of the ram caused great activity in the pyloric region, and the gravity director head was seen to drop into the second part of the duodenum. There is still some residual air in the stomach.

CASE 2 (No. 799902).—A well-preserved white man of 72 years had a combined abdominoperineal resection for carcinoma of the rectum, and after removal of the rectum a small perforation of the wall was noticed in the specimen. Routine gastroduodenal continuous suction was discontinued four days after operation, and three days later considerable distention of the bowel was evidenced. No bowel sounds were detected and the abdominal wall was tense.

A preliminary attempt to intubate was made with the standard tube, using massive air injection, without success. A tube fitted with the same type of ram as that used in the first case (Fig. 1, *A*) was passed, and for some reason not clear the ram burst before any great movement of the tip of the tube across the stomach could be observed. The patient asked, "What hit me, Doc?" and shortly afterward eructated a considerable amount of gas. A new ram of the same type was attached. After half-inflation of this ram the gravity director head was observed to pass more to the right across the stomach than at the first attempt, as the tube was manipulated at the nose. Shortly afterward the balloon ruptured again. The attempt was abandoned.

During the night the patient had massive bowel movements from the colostomy following the use of bowel stimulants, including stomach explosions, but the distention was not completely relieved. The tube was removed from the stomach and he gave no further anxiety.

However, five days later the extreme distention, with bowel sounds absent, again occurred and the same difficulty was experienced in gaining access to the pylorus by the standard massive air-injection technique.

At this time the patient developed a pleural effusion in the right lower lung field. In the meantime a ram of different design, shown in Fig. 1, *B*, had been fabricated. A parallel balloon designed to inflate from the point of attachment to the tube toward the free end, it was thought, would function better.

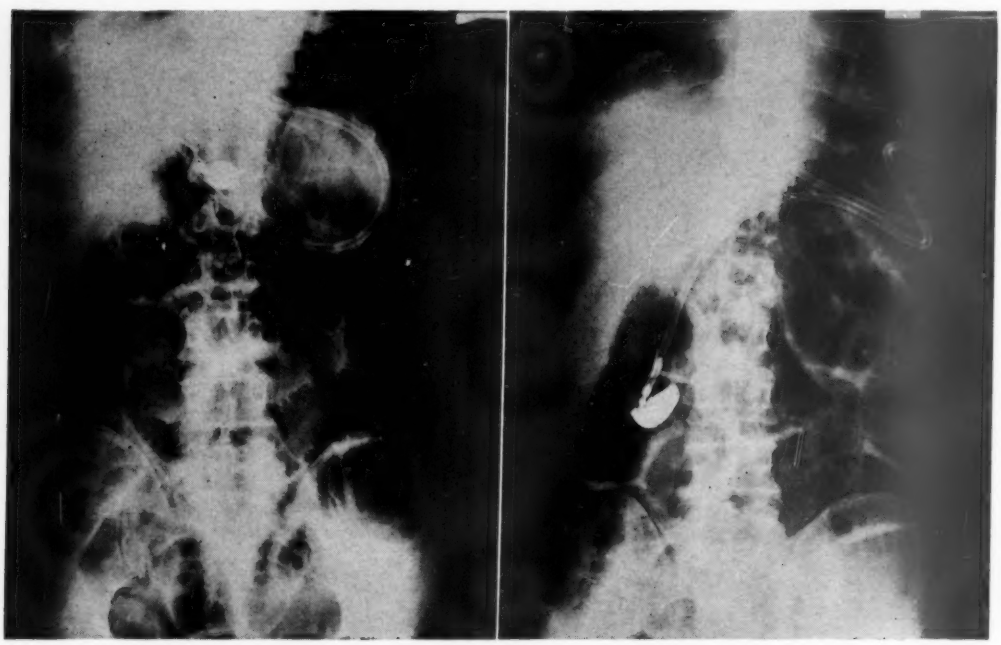

Fig. 4. Fig. 5.

Fig. 4.—The type of "ram" (Fig. 1, *B*) which proved successful in Case 2. The greater curvature of the stomach has been forced down against the pressure of the distended bowel and has resulted in delivery of the tube tip to the pyloric region.

Fig. 5.—The gravity director head is seen in the lowest part of the second portion of the duodenum (Case 2), after manipulating the tip of the tube, shown bent back upon itself in Fig. 4, into the upper part of the second portion of the duodenum. This final position was achieved as the ram was deflated with the patient lying on his back with his feet tilted 45 degrees downward from the horizontal position.

The patient was now extremely ill but still cooperative, and for the fifth time a tube was passed into the stomach. The ram was inflated with air with the patient on the right side under fluoroscopic vision and was seen to pass to the pylorus. At this point the radiograph shown in Fig. 4 was taken. The tip of the tube was straightened out by inflating the intestinal balloon bolus and was seen to slip into the upper part of the second portion of the duodenum. The intestinal balloon was deflated and the patient was placed at 45 degrees to the horizontal with the feet down. The ram was then allowed to deflate as more tube was swallowed, and the gravity director head was seen to move down into the lower part of the second portion of the duodenum (Fig. 5).

Eight hours later a radiograph showed the tip of the tube past the ligament of Treitz. Continuous gastroesophageal suction through a tube passed into the other nostril was started in order to prevent redistention. By the fourth day following the successful intubation the patient was clinically and radiographically decompressed. On the fifth day the tube was thought to be arrested, so a local bowel enema was given. The barium did not pass on at fluoroscopy but had done so by the next day. No bowel sounds were heard until the tenth day. On the thirteenth day of intubation the colostomy was working well and the tube was removed soon afterward. The patient made an uneventful recovery thereafter.

CASE 3 (No. 799718).—An emaciated white woman of 67 years had a five-year history of ulcerative colitis which was treated three months prior to admission with an ileostomy preparatory to removal of the colon. She was thought to have an intermittent obstruction upon admission, and intubation was considered a wise precaution in view of the few distended loops seen in the radiograph and in view of her vomiting. She was not clinically distended. It was decided to try a ram.

A tube of the same type as that used in Case 2 was inserted into the stomach. The tip of the tube was delivered to the pyloric antrum by air injection. The ram was inflated and the tip of the tube was delivered into the first part of the duodenum but could not be delivered further. The tube took forty-eight hours to travel round to the ligament of Treitz.

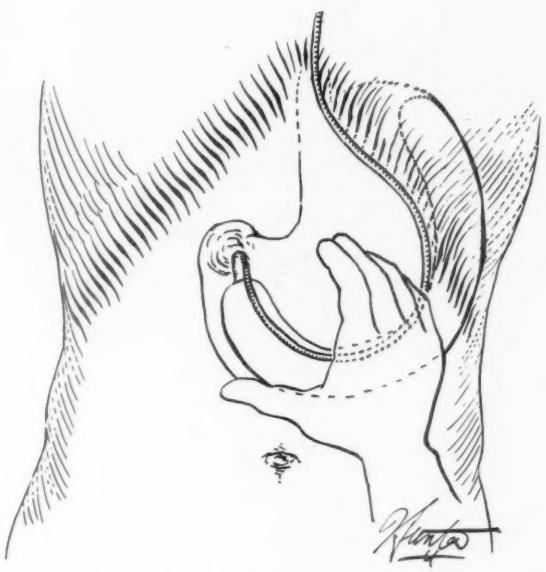

Fig. 6.—A representation of the principle of manipulating the inflated ram shown in Fig. 1, *C*, through the abdominal wall under fluoroscopic control. This principle was used in Case 3, in which almost no distention of the bowel was present. Where great bowel distention is present the pressure of the hand is replaced by the upward pressure of the distended bowel.

By this time it had been decided to let the tube travel down the bowel in order to permit of an unhurried opening of a new ileostomy, following upon a proposed colectomy with revision of the ileostomy. Unfortunately the tubing developed a kink. This tubing* of the Honor-Smathers type was brown in color instead of white. It had a larger aspirating lumen and the same wall thickness so that it was even more prone to kinking than was the original white Honor-Smathers tubing. Since the operation had been delayed it was deemed advisable to remove this tube, because it would give rise to trouble when the time came for bowel drainage.

This gave the opportunity to fabricate a further development designed to push more of the tip of the tube into the duodenum. A ram shown in Fig. 1, *C* was fitted to a standard tube. It will be noticed that a length of this ram is encased in fabric in order to prevent inflation immediately at the point of attachment and for three inches therefrom. This fabric-covered portion was sufficiently flexible to permit easy nasal passage. When inflated it became rigid and of sufficiently small diameter to act as a probe on the end of the gastric portion of the ram. It was thought that it would be possible for the fluoroscopist to manipulate the tip of the tube into the duodenum, since the greater curvature of the stomach would be forced within reach of his fingers by the inflated portion of the ram (Fig. 6).

*Furnished by C. R. Bard Inc., Summit, N. J.

This tube was easily passed into the nasopharynx and into the stomach of this patient. Massive air injection and right-side lying delivered the gravity director head to the pylorus at once. The ram was inflated with air by means of a bicycle type pump as in Case 2, Fig. 4. The gravity director head was then forced into the upper part of the second portion of the duodenum by the fluoroscopist by a stroking action on the ram through the abdominal wall from left to right. The ram was then deflated and a right lateral radiograph shown in Fig. 7 was taken. Six hours later the tube had passed the ligament of Treitz (Fig. 8). The tube was subsequently removed owing to a change in management.

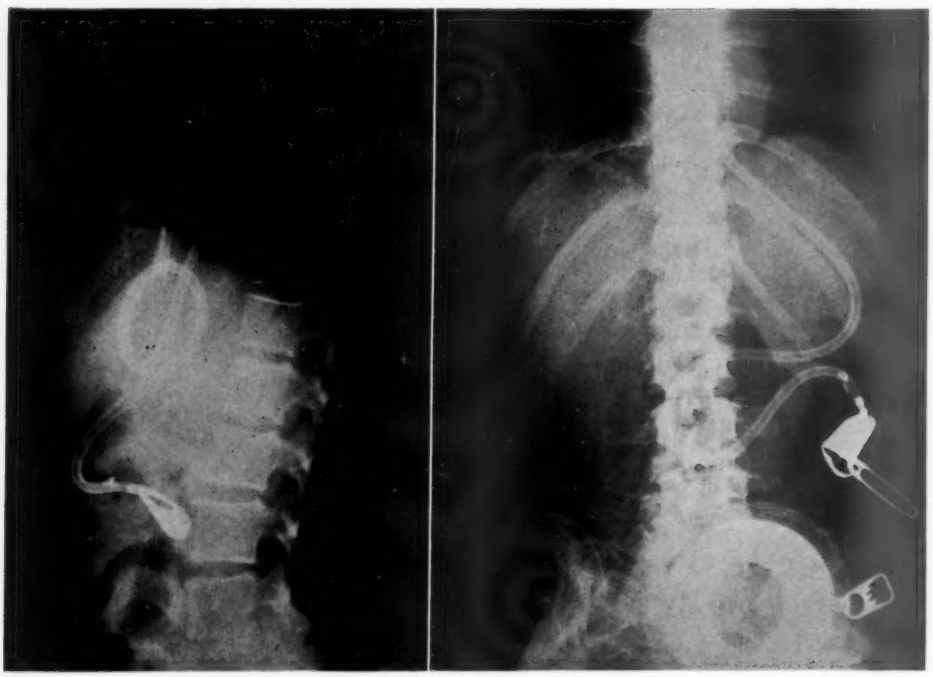

Fig. 7. Fig. 8.

Fig. 7.—A lateral radiograph (Case 3) after the gravity director head had been forced into the duodenum by manipulation of the "ram" through the abdominal wall under fluoroscopic visualization. This patient had an unusually difficult outlet to her stomach, due possibly to either mobility, tortuosity, or both.

Fig. 8.—A radiograph (Case 3) taken six hours after Fig. 7 shows the gravity director head past the ligament of Treitz. The position of the duodenum as outlined by the tube is unusual.

## FURTHER POSSIBILITIES

On the basis of the gastric peristaltic waves observed working on the inflated ram in the first case, it seems possible that such a balloon may enable the stomach as a whole to force the tubes through the pylorus in the presence of good gastric tonus as opposed to the pyloric antrum which at present is relied upon for the purpose. Thus, one balloon bolus only may be necessary, of sufficient capacity to enable the stomach to act upon the tube. Support is given to this concept by Hemmeter[6] who noticed, while taking kymographs of the human stomach, the frequency with which the balloons passed into the duodenum.

The possibility is envisaged of "ramming" all cases where rapid intubation is desirable.

The use of a radiopaque watery fluid is in mind in order to render the ram even more rigid and to facilitate fluoroscopic manipulation. This added weight may also be found advantageous.

SUMMARY

Some developments of the gastric balloon attachment to my standard tube are described, together with the clinical details of their use. Further development is in progress as indicated.

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# CLINICAL OBSERVATIONS ON THE USE OF A HEMOLYTIC AND A NONHEMOLYTIC IRRIGATING MEDIUM FOR TRANSURETHRAL PROSTATIC RESECTION

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TRANSURETHRAL resection of the prostate gland has become a highly satisfactory surgical procedure with a relatively low mortality rate. It is noteworthy that attempts have been made further to reduce mortality and morbidity rates. Efforts have been made in the prevention of hemolytic reactions that may occur with the use of water as irrigating medium. The studies of McLaughlin,[1] Creevy,[2] Landsteiner,[3] and Nesbit[4] have indicated that water can be an etiological factor in the production of postresection oliguria. The concept that the hypotonic irrigating solution (water) can easily enter the blood stream by way of open prostatic veins and produce intravascular hemolysis was first suggested by McLaughlin,[1] and Landsteiner and Finch[3] have shown that as much as 1,000 c.c. of water may enter the blood stream during a prostatic resection. In view of this, the use of nonhemolytic solutions was introduced, so that hemoglobinemia would be prevented. Creevy[5] has used 5 per cent glucose as irrigating fluid and consequently did not find high levels of free hemoglobin in the plasma. Nesbit and Glickman[4] employed glycine solution as an irrigating medium and found it to be nonhemolytic.

In this study a comparison was made between sterile tap water as irrigating medium and glycine solutions prepared with sterile, pyrogen-free, distilled water. Chicago tap water has been found to contain pyrogens.[6] We were interested in the incidence and degree of hemoglobinemia in relation to postresection oliguria and convalescence.

## RESULTS

We first studied 46 consecutive cases in which sterile tap water was used as irrigating medium. Plasma hemoglobin was determined with the Evelyn photoelectric colorimeter by a simple modification of the alkali hemoglobin method for whole blood. Fig. 1 shows the occurrence and degree of hemoglobinemia immediately after operation. Each individual case is represented as a column, and the extent of hemoglobinemia in milligrams per cent of free plasma hemoglobin is indicated on the ordinate. When water was used as the irrigating medium, the postoperative hemoglobinemia in 46 cases ranged from 15 to 1,350 mg. per cent. It is difficult to say at what a level hemoglobinemia may be critical. One may arbitrarily select 100 mg. per cent on the basis of Yuile's[7] work who showed that hemoglobinuria occurred usually when the plasma hemoglobin level exceeded this figure. In the first series of 46 consecutive

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cases, 27 cases (59 per cent) showed plasma hemoglobin values above 100 mg. per cent. Five cases (11 per cent) had plasma hemoglobins above 300 mg. per cent. On the other hand, 11 cases (24 per cent) had plasma hemoglobin below 50 mg. per cent, even though a hemolytic agent, water, was used. The average value for plasma hemoglobin for all cases where water was used was 191 mg. per cent.

In the next consecutive series of 26 cases a nonhemolytic isotonic solution of glycine, as recommended by Nesbit and Glickman,[4] was used as irrigating medium. Only the first 16 cases of this series are shown on Fig. 1 under the heading of glycine. All 26 patients showed a postoperative hemoglobinemia below 55 mg. per cent (from 10 to 55 mg. per cent), with an average value of 29 mg. per cent. Compared with the first series of cases, this represented a marked reduction in hemolysis.

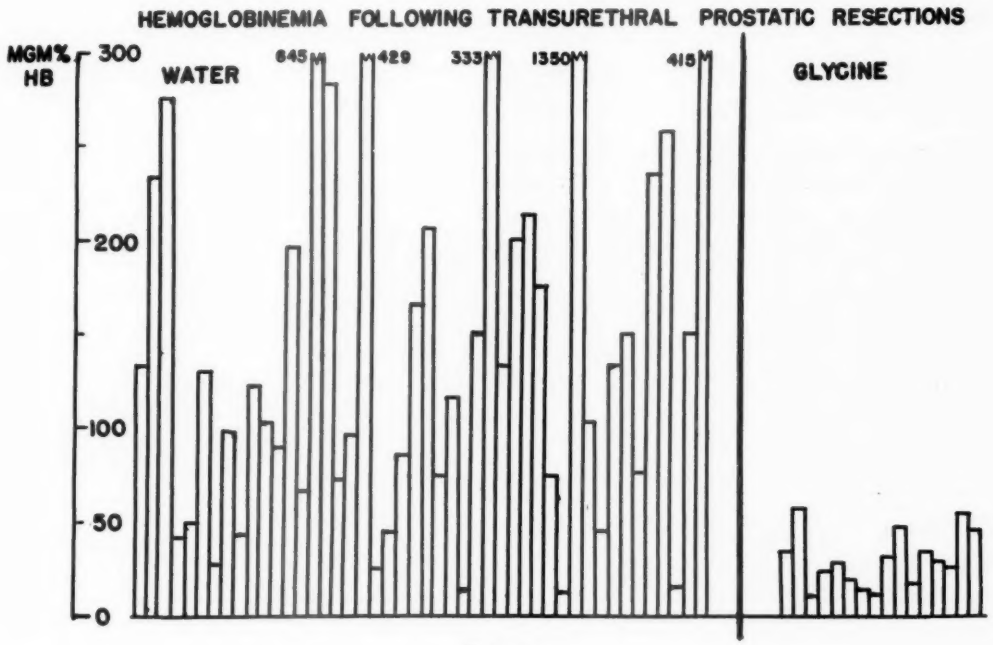


Fig. 1.

DISCUSSION

The use of glycine as an irrigating medium was superior to water in only one respect, prevention of hemolysis. However, with glycine, the resectionist was markedly handicapped by the poor visibility of the operative field. This disadvantage appears to be of greater importance than the prevention of hemolysis.

In this study there was no oliguria or anuria in either series, even in those cases where a significant amount of hemolysis occurred when water was employed for irrigation. The postoperative course was similar in both series; no correlation could be made with high hemoglobinemia and increased morbidity. The patient with the hemoglobinemia of 1,350 mg. per cent had an uneventful postoperative course with a high urinary output, ranging from 900

to 2,500 c.c. daily. On the other hand one patient who had 210 mg. per cent of free hemoglobin in the plasma postoperatively, became progressively more lethargic and listless. Blood urea nitrogen on the eleventh postoperative day was 90 mg. per cent. He recovered slowly and was discharged on the twenty-sixth day after operation with a urea nitrogen of 45 mg. per cent. There was no reduction of morbidity in those patients with free hemoglobin in the plasma below 50 mg. per cent in either series.

Recently, Biorn and Greene[8] studied the pre- and postoperative plasma hemoglobin levels in 100 patients undergoing transurethral resection at the Mayo Clinic. In all these cases sterile water was used as the irrigating medium. They noted hemoglobinemia in 56 per cent of the cases. The only apparent ill effect of this hemolysis was an increase in the frequency of gastrointestinal symptoms in the patients who had high concentrations of plasma hemoglobin as compared with those who did not have hemolysis. One patient in this series developed a postoperative oliguria, but he did not have a significant hemoglobinemia following resection.

We feel that the role intravesical and intravascular hemolysis plays in the production of the postresection oliguria is small and probably of little significance, unless extremely high concentrations of free plasma hemoglobin would occur, such as over 2,500 mg. per cent. It is doubtful whether such high levels can occur following transurethral prostatic resection. Biorn and Greene[8] are also of this opinion. Factors other than hemolysis may produce oliguria and uremia, and they are more important in the consideration of the operation. These factors are age of the patient, previous kidney damage, shock and low blood pressure, excessive blood loss, dehydration, repeated operations, repeated blood transfusions, and operative complications such as perforation of the bladder with extravasation of fluid into the peritoneal cavity or perivesical spaces.

With these factors in mind we have studied the reported cases of death from postoperative oliguria following transurethral prostatic resection. We wish to stress that Nesbit[4] has not observed posthemolytic oliguria in any of the resected patients in the University of Michigan Hospital during the past sixteen years. It is unfortunate that quantitative determination of the degree of hemolysis was not made immediately after operation. Landsteiner[3] determined hemochromogen levels the day following operation. In Creevy's[2] case, the patient had a previous prostatic operation. Immediately after the resection the patient had what was thought to be a toxic reaction to Pentothal sodium and was placed in an oxygen tent. After oliguria had developed, peritoneal lavage was unsuccessful, and sections showed chronic pyelonephritis, together with the typical transfusion kidney. McLaughlin[1] reported 3 cases of oliguria. The first patient was 72 years old, with a preoperative nonprotein nitrogen of 48 mg. per cent. Two hours after transurethral resection, suprapubic cystostomy had to be performed. At post-mortem examination one of the pathologic findings was thrombosis of branches of renal veins. The second patient also had two operations. The second operation showed an ex-

cessive amount of clear watery fluid in the perivesical space. For the first seven days the patient did not have more than 400 c.c. of urinary drainage per twenty-four hours. Although on the eighth day the urinary output rose to 1,200 c.c. the patient died on the ninth day, but autopsy was not performed. The third patient was 74 years old. He also had two operations, the second for a perforation of the vesical neck. Post-mortem examination revealed "hemoglobin" nephrosis, pyelonephritis, actue pancreatitis, and acute necrosis of the liver. In his discussion, McLaughlin pointed out that in each of these cases there was excessive bleeding. Landsteiner and Finch[3] reported a fatal case of renal failure following transurethral prostatectomy. Before operation the patient had a blood pressure of 200/110, urines had specific gravities between 1.006 to 1.012, and contained 3 plus albumin. Following the resection, the hemochromogen level was 199 mg. per cent. On the eighth postoperative day, the urinary output was 1,400 c.c., and thereafter the patient maintained an output of over 2,000 c.c. Autopsy was not performed. Another patient had a higher hemochromogen level (265 mg. per cent), yet had a good recovery and presented no evidence of renal damage or nitrogen retention.

We wish to point out that in the fatal cases quoted here, in addition to hemolysis and postoperative oliguria there were other more important factors that led to death. Creevy's case had three additional factors, namely, previous prostatic operation, previous kidney damage (chronic pyelonephritis), and an operative complication (possible toxic reaction to Pentothal sodium). All of McLaughlin's patients had excessive bleeding. In addition, his first patient had two operations and thrombosis of renal veins. The second had extravasation of clear watery fluid in the perivesical space. McLaughlin's third case had three additional factors, two operations, perforation at the vesical neck, pyelonephritis, acute pancreatitis, and acute necrosis of the liver. The patient of Landsteiner and Finch had extensive previous renal damage and hypertension. During the last four days of his life this patient had diuresis, but developed auricular fibrillation and died of cardiac failure. A patient recently studied by us developed postresection oliguria and a clinical picture typical of lower nephron nephrosis. Blood plasma was examined grossly after resection and was noted to be only faintly red. The patient developed an icterus on the third postoperative day with an elevated serum bilirubin. In this case other factors must have played a dominant role. There was a marked drop in blood pressure after the spinal anesthetic was administered, there was considerable blood loss during the operation, and blood was given to the patient using distilled water instead of saline solution to flush out the transfusion tubing.

We feel that the prevention of hemolysis will not eliminate the occasional postoperative oliguria following transurethral prostatic resections. Numerous clinical and experimental observations have shown that hemoglobinemia alone will not produce fatal renal insufficiency. In experiments on dogs we have

observed a fatal uremic death after eight days of complete anuria in an animal with an initial degree of hemoglobinemia of 1,300 mg. per cent. Another dog recovered completely after an initial hemoglobinemia of 6,200 mg. per cent. Other factors aside from the degree of hemolysis were responsible for the difference in the outcome.[9]

As stated before, the resectionist was markedly handicapped by the poor visibility of the operative field when glycine was used as irrigating medium. This was caused by the clouding effect of intact red cells suspended in the glycine solution. Only the most experienced surgeon was able to finish a resection with the use of glycine irrigation. Water, by rapidly hemolyzing the red cells, produces a superior visual field. Therefore, it is of distinct advantage to have an irrigating medium that will hemolyze red cells. Without this, complications may occur, the most serious and most frequent being perforation of the bladder. Ebert and Barett[10] have suggested the use of 1.8 per cent urea solution as an irrigating fluid to improve the visual field. They have used it in 227 successive transurethral resections without producing any untoward effects on the patient. Urea is known to be highly hemolytic in vitro and hemoglobin is readily solubilized by it.

On several occasions it was necessary to switch to water when glycine was used, in order to obtain a better visualization of the operative field. We feel that prevention of perforation of the vesical neck is more important in reduction of mortality than prevention of hemolysis. The use of any irrigating medium, whether glucose, glycine, or saline, will have the same disadvantage if that solution prevents hemolysis, and it may lead to a higher incidence of perforations of the vesical neck. Because of this difficulty we have reverted to the use of sterile water as the irrigating solution during resection. We should like to emphasize that even more important than the prevention of hemolysis is the prevention of shock, excessive hemorrhage, and postoperative anemia. This can be prevented by the routine use of whole blood transfusion at the start, during, and immediately after operation. If the hemodynamics of the body are maintained, the products of hemolysis do not seem to have a deleterious effect.

One may take certain precautions to prevent excessive hemolysis when water is used as an irrigant. The height of the irrigating column should be adjusted to allow a good flow through the resectoscope without causing an excessive head of pressure in the prostatic urethra; a height of the irrigation container of two feet above the patient is usually sufficient. Hemostasis should be carefully accomplished during the resection. The resection should not be carried too deeply into the true prostatic capsule, for herein lie the large venous sinuses which act as portals of entry for water, bacteria, and cellular debris. It has been our experience that when these sinuses are opened, the bleeding is best controlled with a hemostatic bag. Further coagulation only widens the sinus and thus permits more water and hemolyzed blood to enter the circulation.

## CONCLUSIONS

When water was used as irrigating medium in transurethral prostatic resection, the degree of postoperative hemoglobinemia varied from 15 to 1,350 mg. per cent.

The use of glycine as irrigating medium prevented this hemolysis, and postoperative hemoglobinemia ranged from 10 to 55 mg. per cent.

There were no cases of oliguria or anuria in either series.

Morbidity was similar, whether water or glycerine was used.

Water, by hemolyzing the red cells in the bladder, produced a better visual field for the resectionist.

Prevention of hemolysis by use of nonhemolytic solutions may not prevent most of the cases of postoperative oliguria following transurethral prostatic resection.

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# INTRAVENTRICULAR EXTENSION OF AN ANEURYSM OF THE ANTERIOR CEREBRAL ARTERY

## Report of a Case With Successful Removal

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THE recognition of the presence of an intracranial aneurysm prior to its rupture or before profuse intracranial hemorrhage has occurred is an important factor in the treatment of such lesions. The case of a patient presenting subacute manifestations of an aneurysm which originated from the left anterior cerebral artery and eroded through the wall of the contralateral cerebral hemisphere to assume an intraventricular position warrants careful consideration not only because of the unusual clinical picture but also because intraventricular extension of an aneurysm is an exceedingly rare occurrence. This case will be described in detail later.

An aneurysm of a cerebral artery usually manifests itself initially in a violent manner suggestive of the escape of a relatively large amount of blood into the subarachnoid space with localized and generalized irritation of the central nervous system and its coverings. This is less characteristic of aneurysms of other intracranial vessels, such as the internal carotid and basilar arteries, in that they are more likely than aneurysms of the cerebral arteries to be manifested first by some localizing neurologic sign. Cushing[1] and others[2-8] have emphasized that a sacculated intracranial aneurysm rarely reaches sufficient size prior to rupture to give symptomatic manifestation of its presence, although at the time of rupture or shortly thereafter, evidence of compression of a cranial nerve or similar localizing signs may develop. A small percentage of the patients with such a defective aneurysm may complain only of a moderately severe headache and the diagnosis is made solely because this symptom is persistent enough so that a lumbar puncture is performed and bloody or xanthochromic cerebrospinal fluid is found. It seems apparent that a goodly number of such cases may not be diagnosed because the defect in the wall of the vessel is so small or the relation of the aneurysm to the vessel is such that the escape of blood soon ceases.

The "neighborhood" signs[2] of an intracranial aneurysm, consisting of evidence of compression of one or several cranial nerves, some area of the brain, or the pituitary gland, or of erosion of the skull, are most likely to be observed if the lesion involves the intradural portion of the internal carotid artery or the basilar artery. Beadles,[9] in a review of 555 cases of aneurysm of the intracranial arteries, reported that 69 per cent of those with an aneurysm of the "cavernous" portion of the internal carotid artery exhibited such signs. Although he did not give the percentage of patients with an aneurysm of the basilar artery who demonstrated such signs, he did state that an aneurysm of the basilar artery produced these signs in his series more consistently than "any other artery at the base of the brain." The manifestation of an an-

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eurysm of the proximal portion of a cerebral vessel by pressure on one of the cranial nerves or erosion of bone is not uncommon; however, it seems extremely unusual for one at any point on a cerebral artery to make itself evident by pressure on a cerebral hemisphere. The "neighborhood" signs which may be produced by an aneurysm of the anterior cerebral artery or of one of its branches, as described by Critchley,[6] include homolateral reduction in olfactory and visual acuity, paresis of intraorbital muscles, and hypesthesia in the distribution of the ophthalmic division of the trigeminal nerve. Beadles, however, following analysis of his extensive series, concluded that, of those patients who had had an aneurysm of the anterior communicating or anterior cerebral artery, the number who presented definite evidence of neurologic dysfunction attributable to pressure of neurologic structures by the aneurysm was so small and the symptoms were so vague, that the clinical diagnosis of such a lesion was impossible. Of the total group of 555 cases, 37.11 per cent were believed to have presented some evidence of an intracranial aneurysm prior to those of apoplexy. Beadles stated, however, that in many of these cases the symptoms were so trivial, such as headache and sensations of giddiness, that only in retrospect could they be considered as probable manifestations of an aneurysm. Fearnsides[10] described 31 cases in which there were 36 aneurysms of the intracranial arteries due to noninflammatory changes in the media, and 13 cases in which there were 15 intracranial aneurysms apparently caused by an infective embolism. Death occurred shortly after manifestation of the lesion by intracranial hemorrhage in 25 cases in which the aneurysm seemed secondary to noninflammatory changes and in 10 of those in which the aneurysm appeared to have resulted from an infective embolism. Twenty-three were located on a middle cerebral artery, 6 on an anterior cerebral artery, and 1 at the junction of the right posterior cerebral and posterior communicating arteries. Nine were situated at the junction of an anterior cerebral and the anterior communicating artery. Beadles concluded that cerebral aneurysms which do not rupture rarely give rise to symptoms. An analysis of 32 cases of intracranial aneurysms by Garland[11] revealed that 84.3 per cent of the group had died from rupture of the aneurysm; the remainder apparently had never presented evidence of such a lesion and the aneurysm was observed only incidentally at autopsy following death from some unrelated cause. Fourteen of the aneurysms were on a middle cerebral artery, 3 on an anterior cerebral artery, and 3 on a posterior cerebral artery.

McDonald and Korb[12] analyzed 1,125 cases of intracranial aneurysms collected from the literature, in 1,023 of which the location of the aneurysm was given. Two hundred ninety-four, or 28.7 per cent, were located on the middle cerebral artery; 121, or 11.8 per cent, on the anterior cerebral artery or at its junction with the anterior communicating artery; and 30, or 2.9 per cent, on the posterior cerebral artery. In 862 cases there was definite evidence that the aneurysm had ruptured and its location was described in 786 cases. Two hundred forty-seven, or 31.4 per cent, of the ruptured aneurysms were located on the middle cerebral artery; 103, or 13.1 per cent, on the anterior cerebral artery or at its junction with the anterior communicating artery; and 23, or

2.8 per cent, on the posterior cerebral artery. Unfortunately, the cases were not analyzed relative to the proportion which exhibited evidence of the lesion prior to that of subarachnoid hemorrhage.

Dandy's[13] carefully studied series of 120 patients with intracranial aneurysm included 22 with an aneurysm of a middle cerebral artery, 14 with an aneurysm of an anterior cerebral artery and 2 with an aneurysm of a posterior cerebral artery. Of this group, only 2 apparently presented symptoms which might have been associated with the aneurysm previous to evidence of rupture. Each had an aneurysm of a middle cerebral artery. One had had frequent attacks of dull, frontal headaches and almost daily for a period of fifteen years petit mal attacks with loss of consciousness. The other had mild generalized headache for one year prior to exhibiting the acute signs and symptoms of intracranial hemorrhage which ended fatally after five weeks. Five of those with an aneurysm of the middle cerebral artery and one with an aneurysm of the posterior cerebral artery died of other causes without having presented evidence of the aneurysm; one, however, died of hemorrhage from an aneurysm of an anterior cerebral artery.

A review of the observations of these and other investigators reveals that although the "neighborhood" signs of Symonds[2] are commonly associated with an aneurysm of the internal carotid or basilar artery, they are only rarely manifested by an aneurysm at any of the other usual sites. Furthermore, although Symonds stressed the fact that rupture of the aneurysm may result in loss of only a small amount of blood with comparatively mild manifestations of the lesion, this usually precipitates an acute episode. Even though the amount of blood lost is small, he believed there is almost always at least a transient loss of consciousness. It appears that more careful appraisal of cases which would fit into this category with the specific diagnostic procedures for intracranial aneurysm might represent a major step forward in the treatment of such lesions.

Since the introduction of angiography by Moniz,[14] the exact location and operability of an intracranial aneurysm, of course, usually are determined by this method. The aneurysms which have been identified by means of intracranial air visualization, in most instances, were believed preoperatively to be neoplasms. Dandy[13] reported 3 cases of supratentorial aneurysms which were identified in this manner. In 2, the filling defect involved the third ventricle; in the third, the right lateral ventricle failed to fill and the third ventricle and the left lateral ventricle were shifted to the left. The anterior communicating artery was the site of the aneurysm which encroached on the third ventricle in one case and the anterior cerebral in the other. The aneurysm which prevented visualization of the right lateral ventricle had originated from the homolateral middle cerebral artery. In each case, acute symptoms had been precipitated by hemorrhage.

As already mentioned, few aneurysms of the cerebral arteries develop to a sufficient size to be manifested primarily as spacetaking lesions without having previously made themselves evident by an episode of subarachnoid hemorrhage. Therefore, it is not surprising that the number of aneurysms reported

to have been localized by pneumoencephalography or ventriculography is small. On the other hand, it is not to be assumed without reservation that bloody cerebrospinal fluid of nontraumatic origin means that angiography is the most critical diagnostic procedure available. As is well known, such cerebrospinal fluid may be a manifestation of blood dyscrasias, intracranial hemangiomas, degenerative vascular changes within any intracranial neoplasm, or the end result of progressive weakening of the wall of a vessel by atheromatous changes.

The incidence of failure to visualize certain types of aneurysm by intravascular injection of radiopaque substances probably is fairly high. Obviously, a saccular aneurysm filled largely with an organized clot would not be expected to be well visualized in a large percentage of cases. The relatively complete isolation of the vascular annex from the parent arterial lumen may result in little or none of the injected substance entering the aneurysm. Pneumoencephalography or ventriculography may be valuable supplementary methods of examination in such instances, especially if the aneurysm is peripheral to the arterial circle. This is particularly true if, in addition to attacks of bleeding into the subarachnoid space, the patient presents a history and findings suggesting localized cerebral dysfunction. This, of course, may mean that the aneurysm is unusually large or in a particularly strategic position to produce such a clinical picture, or that an intracerebral hematoma, or a hematoma which has remained circumscribed in the subarachnoid space, as in the lateral cistern, has developed.

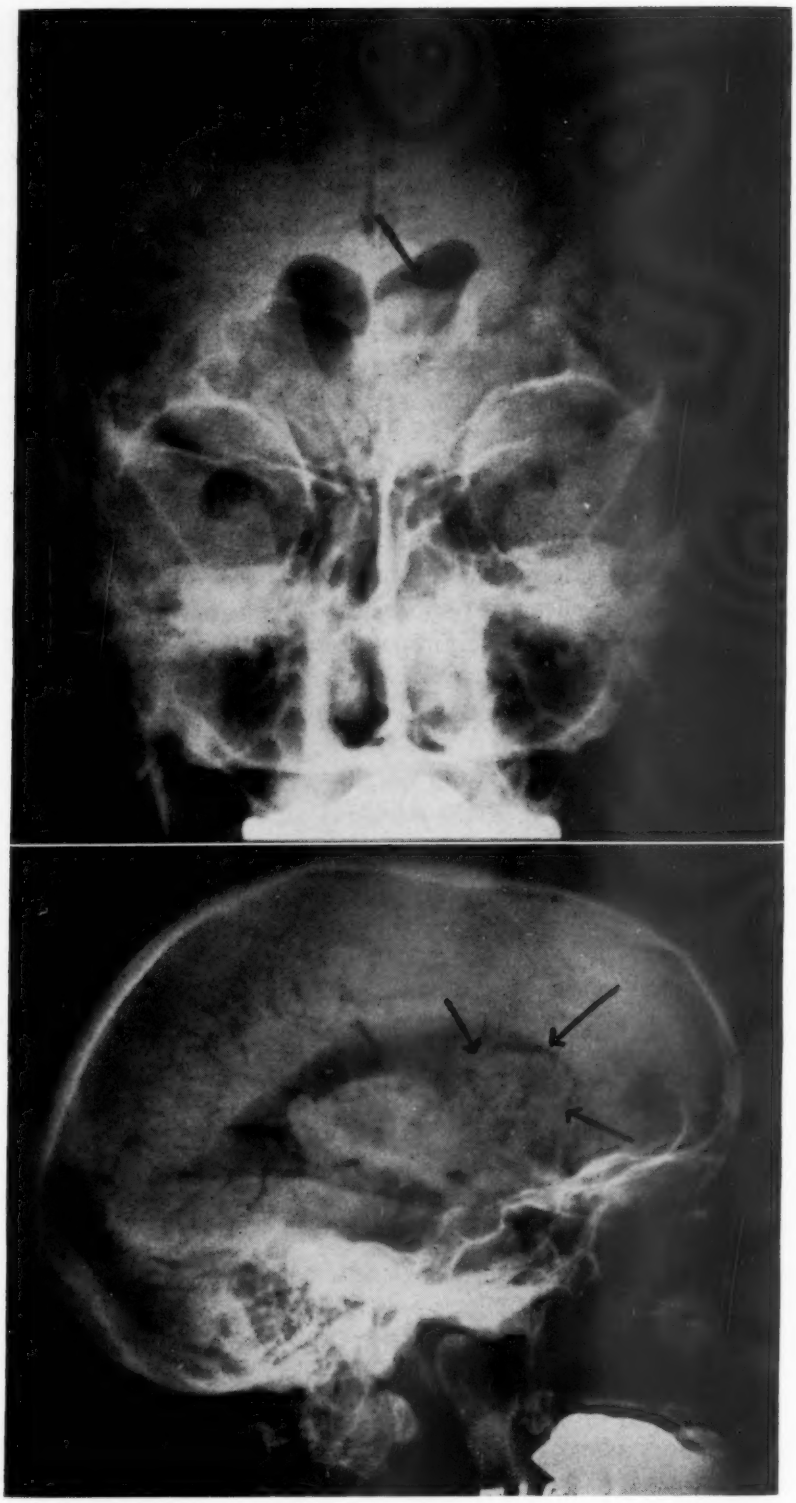
The foregoing brief discussion of the manifestations and methods of identification of an aneurysm of the cerebral arteries serves to emphasize the unusual aspects of the following case from our series of intracranial aneurysms.

## CASE REPORT

Mr. R. S., aged 45 years, was admitted to the Illinois Central Hospital on Oct. 8, 1946, because of a continuous frontal and occipital headache for one month. The onset was sudden and accompanied by a moderate degree of soreness and stiffness of the neck. He had no other complaints of apparent significance, and after two days of rest at home, returned to work. Following three weeks of this persistent discomfort, he was advised to enter his company's hospital located approximately 150 miles from his home. A week elapsed between his departure from home and his arrival at the hospital. He stated that he was unable to recall events during this interval, but further investigation revealed that most of this period had been spent in a near-by hotel with a woman whom he had met on his trip to the hospital. His family had suspected similar irregularities in his behavior for at least two years prior to hospitalization and his wife revealed that during the same period he had shown a greatly increased desire for sexual intercourse.

Except for the apparent inability to recall some recent events and the complaint of bilateral frontal and occipital headache, there was no evidence of pathologic alterations of the central nervous system. However, puncture of the lumbar subarachnoid space, with the patient in the usual recumbent position, revealed an opening pressure of 225 mm. of cerebrospinal fluid. The fluid was xanthochromic. Results of tests for syphilitic infection on both the cerebrospinal fluid and the blood were negative. Except for slight elevation in the cell count and protein content, the cerebrospinal fluid survey revealed nothing significant. Removal of 15 c.c. of fluid reduced the pressure to 150 mm. of cerebrospinal fluid and resulted in several hours of relief from the headache, which then returned to its previous severity.

*A.*

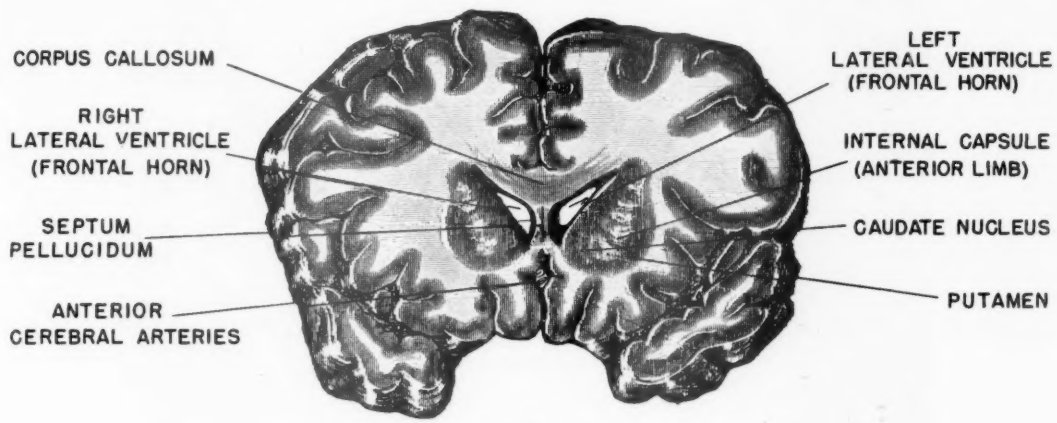


*B.*

**Fig. 1.**—*A*, Anteroposterior view of pneumoencephalogram showing mass encroaching on left lateral ventricle and obstructing view of third ventricle. *B*, Right lateral view of pneumoencephalogram showing mass in frontal horn of left lateral ventricle.

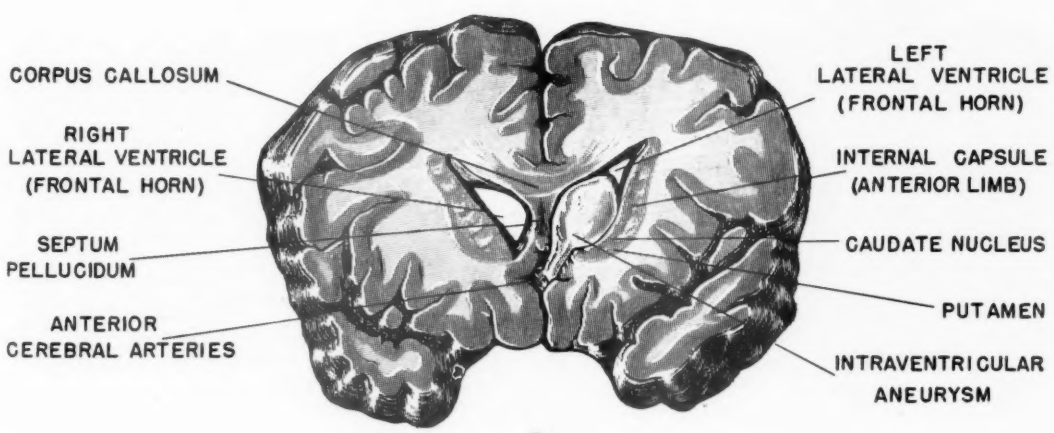
In view of the absence of definite lateralizing neurologic signs but with a history suggestive of defective frontal lobe activity and with only slight elevation of the intracranial pressure, it was decided to make a spinal air injection. The pneumoencephalogram revealed a filling defect of the frontal horn of the left lateral ventricle with slight encroachment on the medial portion of the frontal horn of the right lateral ventricle (Fig. 1, *A*). Both lateral ventricles were slightly enlarged. The third ventricle was not visible on the anteroposterior projections. The lateral projections revealed the tumor to be relatively discrete and within the frontal horn of the left lateral ventricle (Fig. 1, *B*).

At operation on Oct. 15, 1946, the frontal horn of the left lateral ventricle was entered through an incision in the middle frontal gyrus anterior to the premotor area. Visualization of the interior of the ventricle revealed an encapsulated mass approximately 3 cm. in




A.

USUAL RELATION OF ANTERIOR CEREBRAL ARTERIES TO CEREBRUM, ANTERIOR TO THIRD VENTRICLE.




B.

RELATION OF ANEURYSM TO ANTERIOR CEREBRAL ARTERY AND CEREBRUM.

Fig. 2.—Drawing showing (*A*) normal relation of anterior cerebral arteries to cerebrum, anterior to third ventricle and (*B*) relation of aneurysm to anterior cerebral artery and cerebrum in case described.

diameter, which was easily isolated from the adjacent tissue. The mass which was attached to the anterior cerebral artery or to one of its branches was an aneurysm filled with a clot. The aneurysm had eroded through the wall of the cerebral hemisphere in the region of the parolfactory area, the subcallosal gyrus, and the rostrum of the corpus callosum (Fig. 2). The attachment of the aneurysm to the parent artery proved to be insecure and mobilization of the mass resulted in its being torn from the artery. The profuse bleeding which occurred momentarily was stopped by the application of a single silver clip on the neck of the aneurysm (Fig. 3).

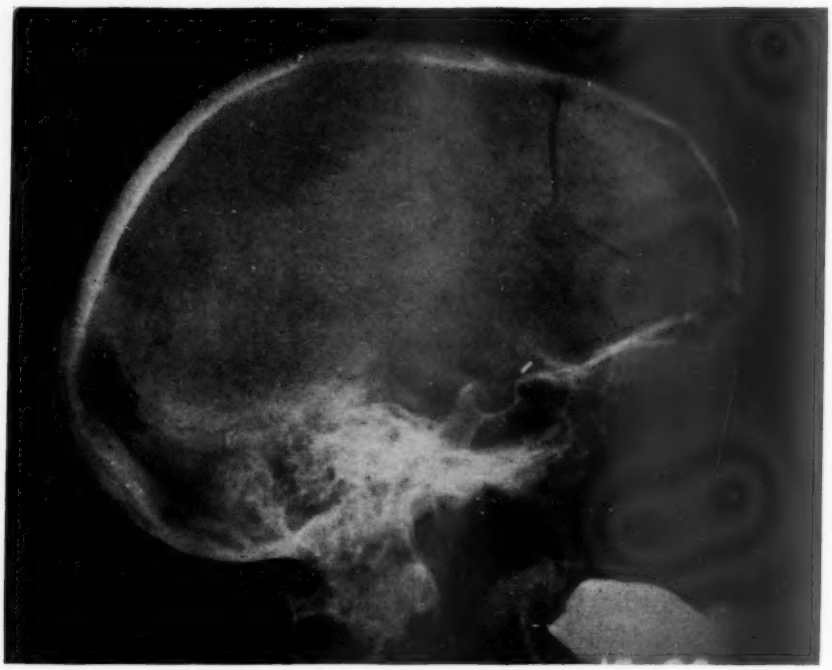


Fig. 3.—Postoperative roentgenogram of skull showing silver clip in place.

Within a few minutes after completion of the operation, which was done with the use of Avertin anesthesia supplemented by sodium pentothal, the patient answered questions readily and exhibited no proprioceptive or exteroceptive deficits. Voluntary and reflex motor activity was intact with only a slight degree of contralateral weakness which disappeared within forty-eight hours. The postoperative course continued smoothly and the patient was discharged from the hospital on the twelfth day following operation. Except for signs of slightly defective frontal lobe cerebration evidenced by transient mild sensations of unreality and by the presence of a slight degree of euphoria, there were no neurologic deficits apparent.

The patient returned to his job as an inspector of locomotives approximately ten weeks following removal of the aneurysm and has worked regularly during the subsequent two years. He has continued to demonstrate the same manifestations of frontal lobe dysfunction. The most unusual feature of his behavior still is the pronounced sexual hyperactivity. There has been no recurrence of symptoms suggestive of bleeding into the subarachnoid space.

## SUMMARY

Reports of several series of intracranial aneurysms are reviewed with particular consideration to those of aneurysms originating from the cerebral arteries.

An unusual case of aneurysm of the anterior cerebral artery is described. Interesting features of the case include the following:

1. An analysis of the case reveals that the aneurysm had undoubtedly been manifesting itself clinically by pressure on the brain for a period of at least two years.

2. Although the aneurysm arose from the proximal portion of the anterior cerebral artery, it had not involved cranial nerves or adjacent bone but had eroded the wall of the cerebral hemisphere and entered the lateral ventricle.

3. The aneurysm had undoubtedly manifested itself for many months by increased sexual activity.

4. When the wall of the aneurysm finally became defective, only a relatively small amount of blood escaped before the defect became occluded. However, repeated small quantities of blood probably escaped during the month between the first evident hemorrhage and removal of the aneurysm.

5. Pneumoencephalography was well tolerated and adequately demonstrated the lesion.

6. Removal of the aneurysm by a transventricular approach was followed by complete freedom from headache and other evidence of bleeding into the subarachnoid space.

7. Evidence of some frontal lobe dysfunction has persisted.

8. The increased sexual activity exhibited as an apparent clinical manifestation of a lesion in the parolfactory and adjacent areas is of interest but to conclude that this may have been due to injury to the anterior portion of the hypothalamus or to the cerebral hemisphere or to both would be unwise without more adequate inspection of the involved areas.

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# INTRAMEDULLARY FIXATION OF FRACTURES OF THE HUMERUS BY THE LONGITUDINAL PIN

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INTRAMEDULLARY fixation of fractures has now been used by us in nearly 100 cases over a thirteen-year period. It has been used in nearly all of the long bones of the body. Although fraught with certain dangers, it has been found to be more physiologic than other forms of treatment when properly and cautiously used.

The purpose of this communication is to review fourteen consecutive cases and to describe a satisfactory technique for pinning fractures of the humerus.

In 1933, when the hanging cast for fractures of the humerus was first described by us[1] and almost simultaneously by John Caldwell,[2] it was presented timidly because of its revolutionary nature. The popular concept of fracture treatment at that time was that it was essential to immobilize one joint above and one joint below the affected shaft. We realize now that the constant pull of the longitudinal muscles of the upper arm acts favorably upon healing by compressing the bone ends. Although by this method traction was exerted only when the patient was ambulatory and the position of the bone was not accurately maintained, non-union of the humerus became less frequent and muscle atrophy of the deltoid and periarticular adhesions of the shoulder became greatly minimized. The hanging cast has taught us the value of permitting free function of the muscles and the avoidance of joint stiffness and made possible the abolition of the shoulder spica and the aeroplane splint.

As a corollary it soon appeared obvious that the contractile power of the muscles of the upper arm was less than generally believed, and most non-union in fractures of the humeral shaft was due to distraction of the bone ends from too vigorous traction rather than from lack of immobilization.

In 1939, in keeping with this idea and having utilized the longitudinal pin principle for the intramedullary fixation of fractures of the ulna[3] and a fracture of the shaft of the femur,[4] we adapted the method to fractures of the upper end of the humerus and a special pin was constructed for this purpose. The use of this pin, while crude in its original form, impressed upon us the possibility of accurately reducing and immobilizing the shaft of the humerus without limiting the function of the extremity. The process of evolution of the procedure, which is now adapted to all the long bones of the body, has been recently described by us elsewhere,[5] and a new longitudinal pin for this purpose has also been recently described.[6]

The use of the longitudinal pin consists of passing a stainless steel pin throughout most of the length of the humerus to transfix the fracture by traversing the medullary canal. The advocated technique requires a specially

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constructed pin with a sled runner type point and a hooked head (Figs. 1, 2, and 3). The pin used for this purpose is made of stainless steel with diameter of three-sixteenths inch and is used interchangeably for both the humerus and tibia.

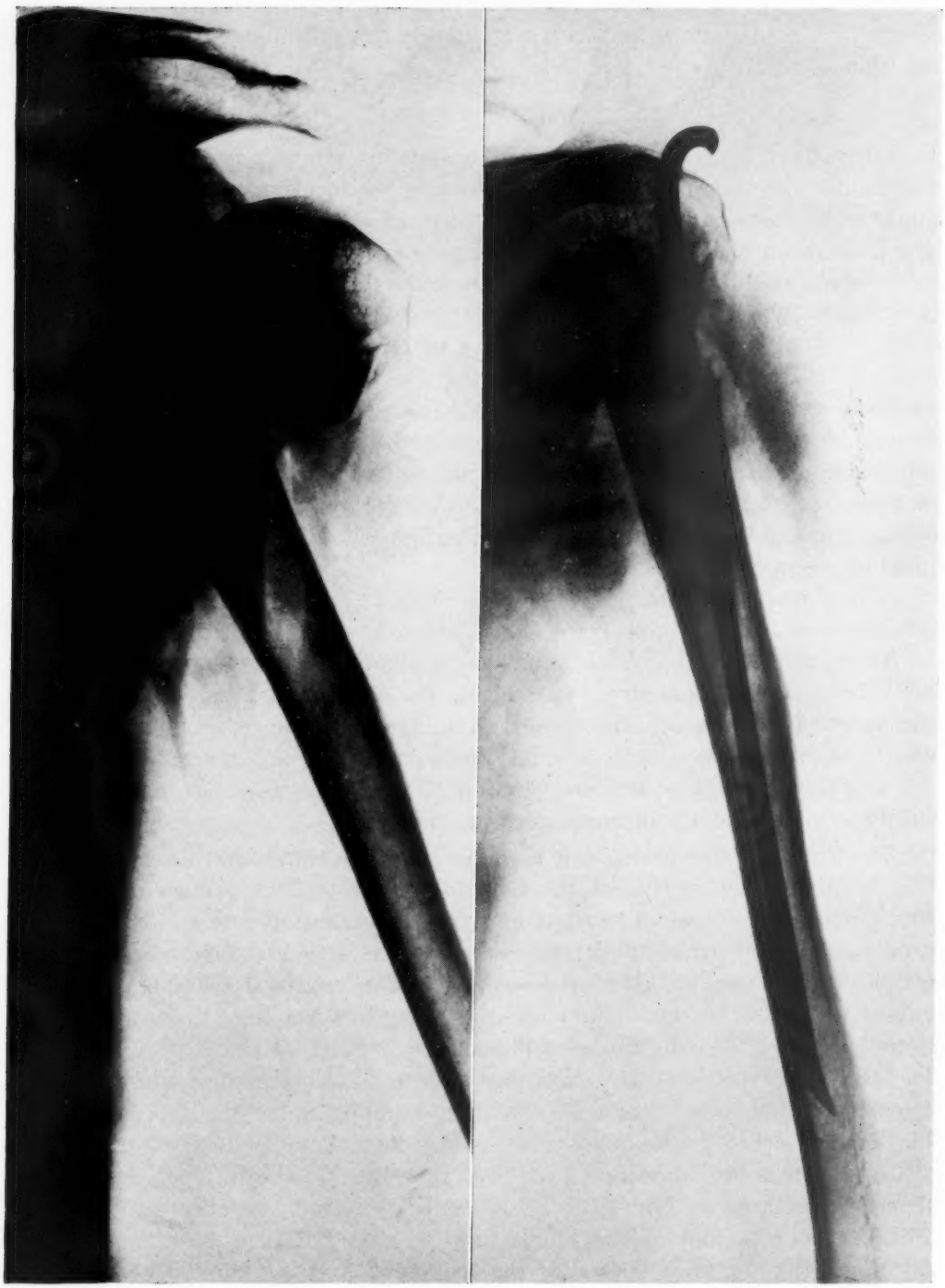
## REVIEW OF CASES

There have been no deaths, no infections, no nonunions, and no evidence of embolism in this series of cases, which is consecutive. Healing has been found to be more rapid than by other methods of treatment, and no deformities have occurred. The accompanying chart (Table I) reviews in detail the fourteen cases in which treatment was by this method to date. The first six patients were treated by the old type pin which was allowed to emit through the skin on the superior surface of the shoulder. The remaining patients were treated by the new type pin, the head of which was buried beneath the deltoid muscle. This permitted the patient's complete comfort with freedom of motion, with the exception that abduction beyond 90 degrees was temporarily limited by the head of the pin striking against the acromion when the arm was in this position. This undesirable feature can be eliminated by sinking the head more snugly against the bone, but this procedure makes removal of the pin slightly more difficult.

## TECHNIQUE

The medullary canal of the humerus is straight for its entire length, ending distally in a conical shape just above the olecranon fossa. A pin of suitable length is chosen by measuring the uninjured humerus from the superior surface of the tuberosity to a point just above the condyles, selecting a pin of this length. It has been found possible to pin fractures of the humeral shaft blindly, but this is not a recommended procedure.

The fracture site is exposed through a minimal incision. In recent cases it is not necessary to dissect the bones subperiosteally. Sufficient exposure only is necessary to remove soft tisue from the bone ends and expose the fractured surfaces. Comminuted fragments are left attached to the surrounding soft tissues. When the fractured surface of the proximal fragment has been properly exposed, a small stab wound is made over the tuberosity of the humerus in line with the fibers of the deltoid muscle. Through this opening a three-sixteenths inch drill is passed to render a slightly oblique opening through the cortex of the bone. The drill is withdrawn and the longitudinal pin of suitable length is then pushed through this opening. Very little resistance is met as it encounters the cancellous bone, but as it reaches the far cortex a definite sense of resistance is felt. The sled runner type point prevents penetration of the far cortex and as the pin is tapped lightly with a mallet it finds its way down the medullary canal of the fragment, and the point is soon seen to emit at the fracture line. It is driven on until about one-half inch of the point is exposed. The proximal fragment can usually be controlled by grasping the pin manually. A bone-grasping forceps then lifts up and angulates the distal fragment and the pin is driven downward into the distal fragment

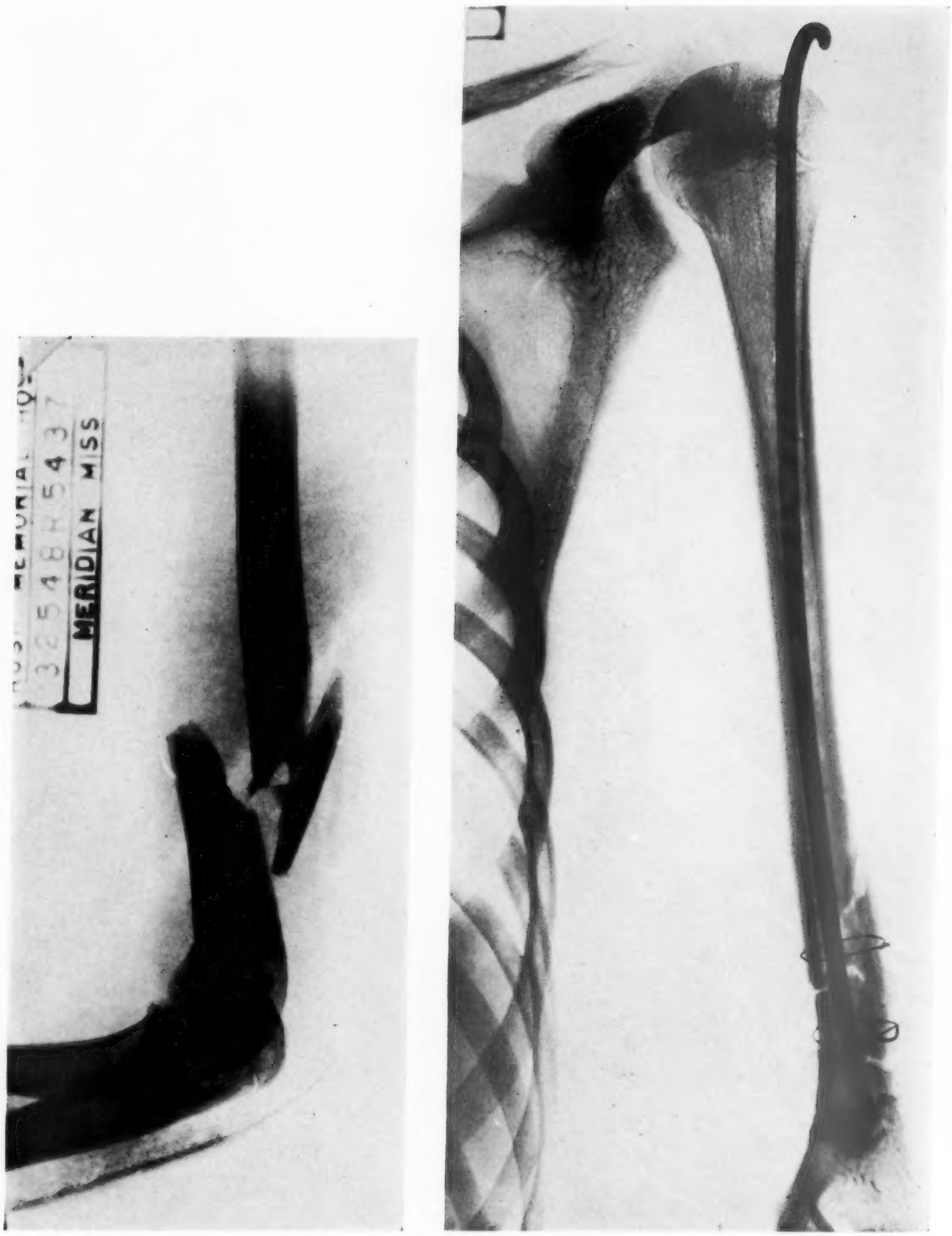


*A.* *B.*

Fig. 1, *A* and *B*.—Comminuted fracture of neck of humerus, before and after pin fixation, open reduction. Immediate function permitted.

*A.* *B.*

Fig. 2, *A* and *B*.—Before and two months after blind pinning of fracture of mid-third of humerus. Immediate function permitted.




*A.* *B.*

Fig. 3, *A* and *B*.—*A*, Comminuted fracture of lower third of humerus. *B*, After fixation by longitudinal pin and encircling wires. Function permitted in ten days.

simultaneous to the realignment of the bone. The fractured surfaces are then properly fitted together as traction is exerted, and it is usually found that the elastic pull of the muscles results in rigid realignment without tendency to angulation or rotation and despite the pull of the muscles, overlapping is impossible.

Comminuted fragments frequently realign themselves due to the tension of the muscle tissues to which they are attached. In the event that the fracture is markedly oblique, the application of encircling stainless steel wires often assures more perfect approximation. In the event that the shaft is

*C.* *D.*

Fig. 3, *C* and *D*.—Anteroposterior and lateral views of humerus eight weeks after pinning operation. (This patient, who had an associated fracture of the tibia, manipulated crutches with this fractured arm within three weeks of the time of operation.)

badly fragmented there will usually be observed an intervening gap through which a portion of the shaft of the pin is exposed. The fragmented pieces of bone are then reconstructed about the pin and held in place with encircling wires. Even in the case of severe fragmentation of the shaft, fixation appears rigid and no form of external immobilization is necessary.

TABLE I. REVIEW OF CASES

| AGE (YR.) | CASE NO. | YEAR | LOCATION | OPERATION | TIME AFTER INJURY | MOTION BEGUN | MUSCLE ATROPHY | FULL ELBOW FUNCTION | SHOULDER ABDUCTION 90 DEGREES | SHOULDER FULL FUNCTION | PIN REMOVED | ULTIMATE RESULT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 15 | 17,141 | 1939 | Neck | Open | 3 Wk. | Immediately | Slight | Immediate | 4 Wk. | 6 Wk. | 4 Wk. | xxxx |
| 14 | 19,526 | 1940 | Neck | Open | 3 Wk. | Immediately | Slight | Immediate | 4 Wk. | 6 Wk. | 4 Wk. | xxxx |
| 21 | 25,171 | 1940 | Neck | Open | 5 Days | Immediately | Slight | Immediate | 4 Wk. | 8 Wk. | 4 Wk. | xxxx |
| 40 | 25,347 | 1942 | Neck | Open | 8 Days | Immediately | Slight | Immediate | 5 Wk. | 8 Wk. | 4 Wk. | xxxx |
| 10 | 25,827 | 1943 | Neck | Open | 2 Wk. | Immediately | Slight | Immediate | 4 Wk. | 6 Wk. | 4 Wk. | xxxx |
| 58 | 33,156 | 1945 | Neck | Closed | Immediate | Immediately | Slight | Immediate | 6 Wk. | 8 Wk. | 2 Wk. | xxxx |
| 14 | 35,731 | 1946 | Neck | Open | 5 Days | Immediately | Slight | Immediate | 4 Wk. | 6 Wk. | 4 Wk. | xxxx |
| 16 | 40,377 | 1948 | Comminuted lower third | Open | 10 Days | Immediately | Slight | Immediate | 3 Wk. | 8 Wk. | 8 Wk. | xxxx |
| 52 | 41,091 | 1948 | Comminuted lower third | Open | 8 Days | Immediately | Slight | Immediate | 3 Wk. | 8 Wk. | 8 Wk. | xxxx |
| 56 | 41,674 | 1948 | Head and neck fragmented | Open | 5 Days | Immediately | Moderate | Immediate | 8 Wk. | -------- | ------ | ---- |
| 56 | 42,094 | 1948 | Neck fragmented | Open | 4 Wk. | Immediately | Moderate | 3 Wk. | 8 Wk. | -------- | 3 Mo. | ---- |
| 29 | 42,137 | 1948 | Mid-third | Closed | Immediate | Immediately | None | Immediate | 2 Wk. | 4 Wk. | ------ | xxxx |
| 49 | 43,191 | 1948 | Head and neck crushed | Open | 8 Days | Immediately | Moderate | Immediate | 4 Wk. | -------- | ------ | ---- |
| 58 | 42,239 | 1948 | Mid-third comminuted compound; mangled extremely | Open | Immediate | 4 Weeks | Moderate | 6 Wk. | 3 Mo. | Severe muscle injuries | 3 Mo. | xxxx (bone) xxx (soft tissue) |

Note: 4 x's denotes good results.

Following the closure of the wound, it has been our custom to bandage the extremity from the bases of the fingers to the armpit with elastoplast applied over cotton batting to minimize swelling.

Plaster splints made by Curity* have an adhesive quality when wet, and it is sometimes felt desirable partially to immobilize the extremity for a few days by molding plaster splints to the external surface of the dressing. As soon as the swelling subsides the dressing is removed and full function of the part is encouraged.

The head of the pin is buried beneath the deltoid muscle. It appears to cause no irritation, but unless the pin is driven fairly flush it will block abduction beyond ninety degrees by striking the acromion process in the scapula.

After several weeks, when the pin has served its purpose, it is removed by making a three-fourths inch incision under local analgesia, exposing the head of the pin which can be palpated without difficulty, and by inserting the tip of a screw driver beneath the hooked head and simply tapping upward with a mallet.

## SUMMARY AND CONCLUSIONS

Fourteen cases of humeral fractures treated by longitudinal pin fixation have been reviewed. In our experiences, fixation of the fracture has been excellent, there has been no tendency to rotation, the presence of the pin in the medullary canal has caused no injury to the patient, nor has he been conscious of its presence. Healing has been much more rapid than by any other method used by us; there have been no nonunions, no infections, and no deaths. The return of function is extremely rapid with the resultant avoidance of muscle atrophy, periarticular adhesions, and joint stiffness. One patient (Fig. 3) who received a comminuted fracture of the lower third of the shaft of the humerus complicated by fracture of the tibia was able to manipulate crutches with the fractured arm within three weeks of the time of the operation.

The technique of the longitudinal pin, while entailing an open operation, has been found to be, from the patient's standpoint, a relatively simple procedure and is applicable to bad-risk cases. While in our concept the choice of treatment in most fractures of the humeral shaft lies between the use of the hanging cast and the longitudinal pin, the marvelous comfort and splendid results with the longitudinal pin method are most intriguing.

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*Bauer and Black (Curity-ostic).

# PRONE POSITION FRAME

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THE prone position is one of the most difficult to obtain in a way which will satisfy both the surgeon and the anesthesiologist. By this time various prone position tables have been designed. Surgeons and anesthesiologists have worked together in planning these tables so that they meet the requirements of the individuals involved. However, from a practical viewpoint they have been lacking because of the following reasons:

1. Most of them are very expensive and therefore are not purchased by many hospitals.
2. They are large, bulky, heavy tables that are not portable and that consume space.
3. They are designed for one type of surgery and are not adaptable to the necessities of other prone positions.

Since these statements are true, we have been interested in developing a frame for the prone position that will meet the following specifications:

1. One that is easily stored and easily handled by operating room personnel.
2. One that is light and easily transportable so that it may be carried from hospital to hospital by the surgeon or anesthesiologist.
3. One on which most of the prone positions may be obtained.
4. One that is the answer to the anesthesiologist's problems; that is, assures free unobstructed breathing, avoids undue pressure on nerves, such as brachial plexus and lateral femoral cutaneous nerves, and avoids altogether pressure on the celiac plexus, sacral plexus, abdominal aorta, vena cava, or iliac arteries or veins.
6. One that gives the surgeon the working conditions he desires.
7. One that is easily adjusted but needs only minor mechanical repairs.
8. One that is inexpensive to construct.

With this as a basis we have been working on various types of prone position frames since 1947. When one of us (L. H. E.) was at the American Academy of Orthopedic Surgeons meeting in Chicago in 1948, he got the idea for the frame we are employing at the present time.‡

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‡Shorbe, H. B.: Bone and Joint Hospital McBride Clinic, Oklahoma City. Exhibit at American Academy of Orthopedic Surgeons January, 1948. Convex Saddle Frame for spine operations.

## DESCRIPTION

The frame is made of 1 inch, ordinary plumbing pipe. It consists of two curved vertical bars which slide on an "H" frame by means of "T" pipe connections which are held in correct position with set screws. This makes the frame adjustable for width only. After experimenting with various lengths, heights, and curvatures, we have arrived at the dimensions shown in Fig. 1. Perhaps it would be ideal for men using these frames to have three sizes, large, medium, and small, with the length and curvature varying. Nevertheless, with the frame as shown here we have operated on patients 5 feet to 6 feet 6 inches tall by merely moving them upward or downward until the desired operating position was secured. The two vertical curved bars are covered with felt and 2 inches of sponge rubber, and this in turn has a Koroseal washable cover.

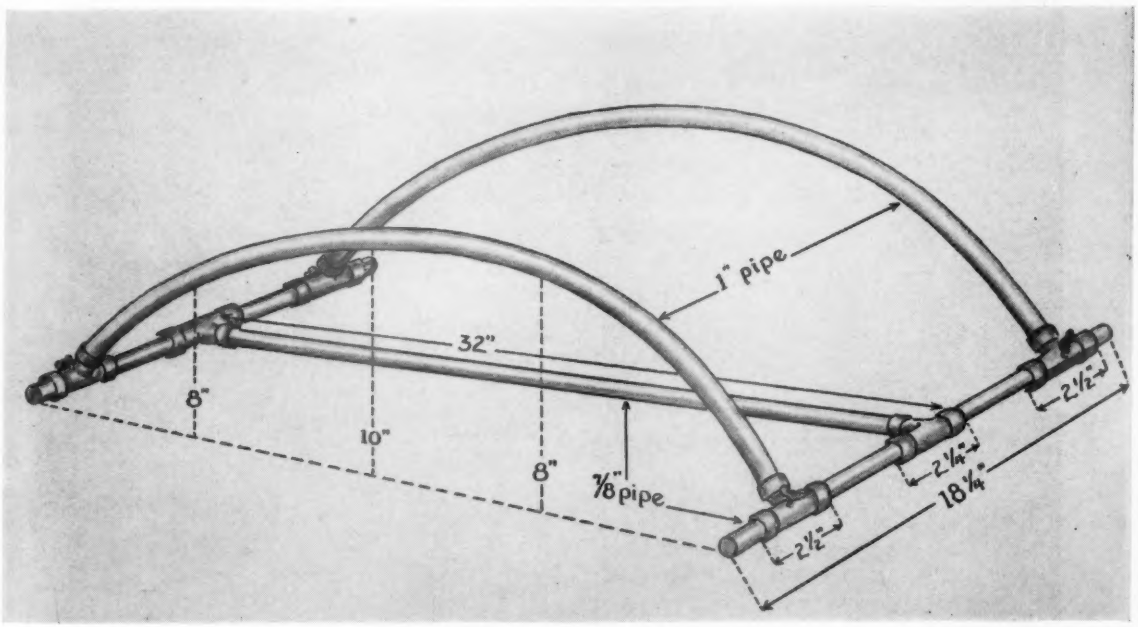



Fig. 1.

## ADVANTAGES

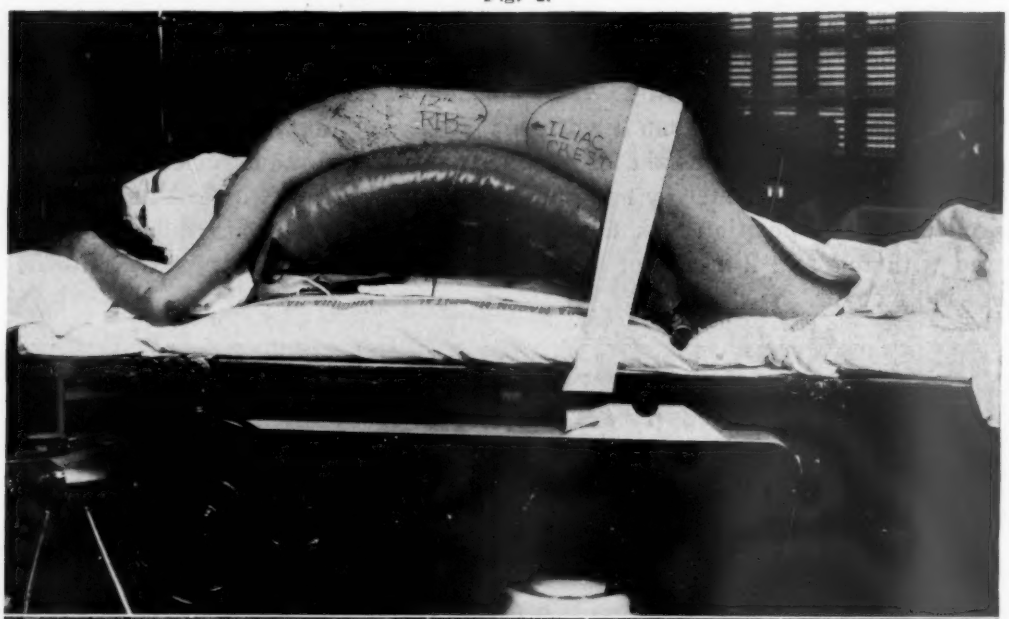
1. All prone positions for surgical procedures may be obtained with the exception of the Overholt chest position and the position for brain surgery. Figs. 2 and 3 show a patient in position for a Smithwick lumbodorsal sympathectomy and a laminectomy with spinal fusion, respectively.

2. No pressure on the major arteries, veins, or nerves is encountered as the patient is suspended between two vertically curved bars (see Figs. 4 and 5). We have never seen positional circulatory collapse or embarrassment with this frame.

3. The surgeons have commented on stability of the patient on the frame. There is no sliding or change of position during pounding or pushing. This is often encountered when pillows, sandbags, bricks, or specially designed tables are used.

4. Respirations of the patient suffer only minimum impairment as the patient is suspended to a large extent by the shoulder girdle and iliac bone. This is true irrespective of type of anesthesia. Smithwick procedures were

Fig. 2.



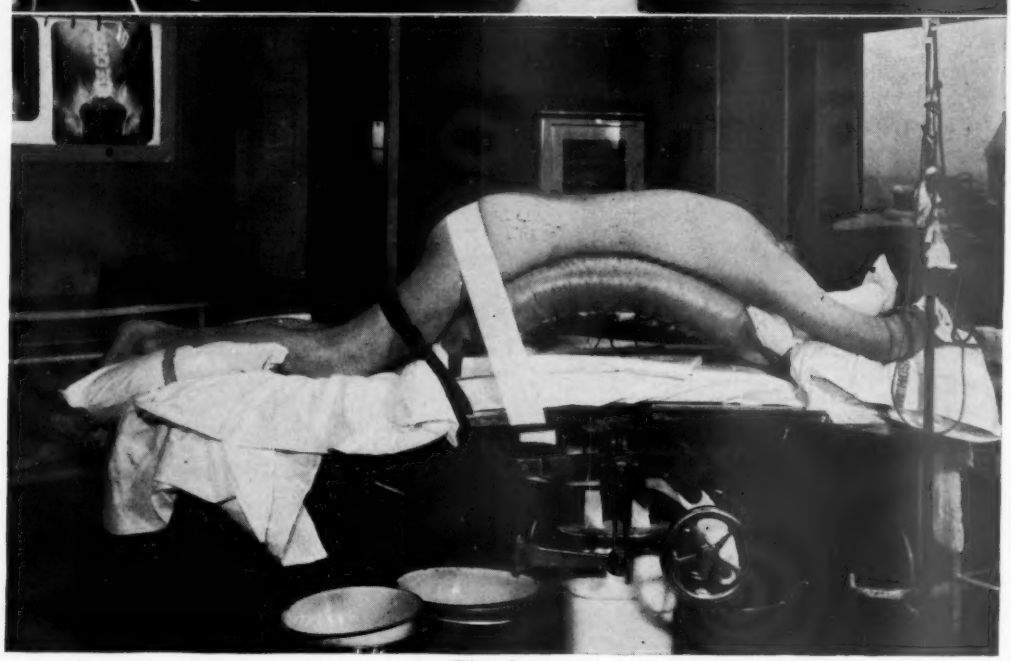



Fig. 3.

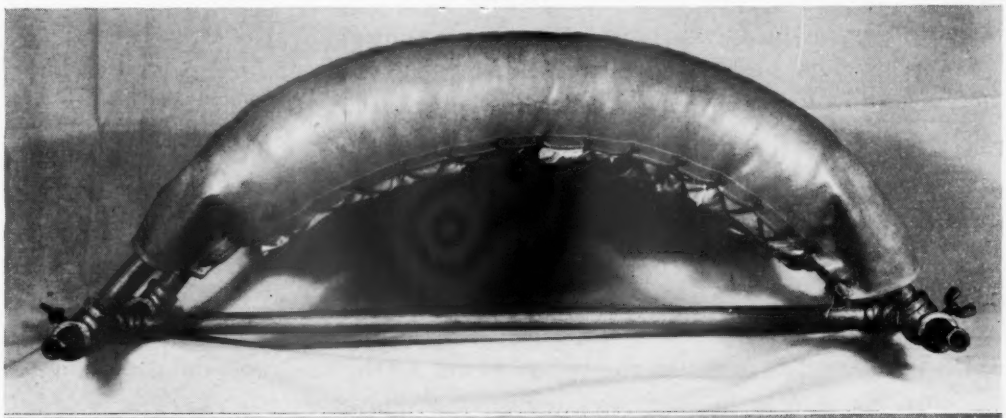
performed under general anesthesia with an endotracheal tube in place (Fig. 2) and laminectomies and fusions were done under subarachnoidal block with 0.2 per cent Sodium Pentothal analgesia (Fig. 3).

5. The frame is light, approximately twenty-five pounds, easily transportable, and may be stored with ease. It fits on any operating room table;

therefore, the patient may be raised, put in Fowler's position or Trendelenburg position, and tilted from side to side.

6. The frame costs only $25 to construct and cover. Our frame was made by the hospital engineer and covered by one of the local brace shops.

Fig. 4.



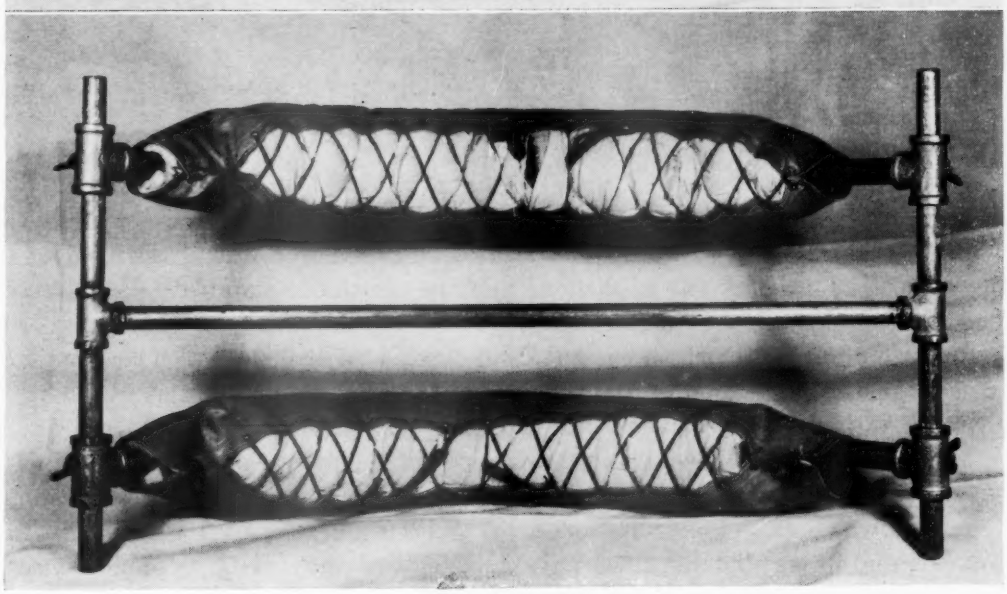


Fig. 5.

## DISADVANTAGES

Pressure bruises may occur over the maximum points of pressure on the iliac crest and the side of the body. These are usually minimal and we have not had tissue destruction or slough.

## CONCLUSION AND SUMMARY

This frame as described has answered both the surgeons' and the anesthesiologists' problems in eighty cases. Fifty-two were laminectomies and spinal fusions, and twenty-eight were Smithwick lumbodorsal sympathectomies. It is far superior to sandbags, pillows, bricks, and rolls as the patient will not move after he has been positioned. Abdominal pressure is avoided. Construction is an inexpensive, simple task.

# A POLYETHYLENE ROD VEIN STRIPPER

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THE purpose of this communication is to introduce a new device for vein stripping in the surgical management of saphenous varices.

We have employed this instrument with considerable facility and technical success at the University Hospitals and believe that it offers advantages over existing instruments.

## DESCRIPTION

The stripping device is a 36 inch extruded polyethylene rod measuring ⅛ inch in diameter. The advancing end is fashioned into a blunt point for introduction through the vein. The other end is flattened slightly and pierced with two holes 1½ cm. apart and large enough easily to accommodate straight Keith needles. The edges of the rod adjacent to the holes are notched to aid in securing the vein to the rod with transfixing ligatures (Fig. 1).

## STERILIZATION

The polyethylene rod may be easily sterilized by immersion in a 1:1000 tincture of merthiolate solution for 30 minutes or by boiling.

## METHOD

Under intravenous sodium pentothal anesthesia a transverse incision is made in the thigh over the saphenofemoral vein junction and carried down to the superficial fascia. The saphenous vein is identified, clamped, and severed. The proximal portion is dissected free from the surrounding tissue, and all branches are carefully clamped, cut, and ligated with 000 silk. The proximal segment of the saphenous vein is then doubly ligated with 00 silk at its point of entrance into the femoral vein, and the excess portion is excised.

The patient is placed in a 20-degree Trendelenburg position. The polyethylene rod is then passed into the lumen of the distal segment of the saphenous vein, and with gentle manipulation we have been able to pass the rod well into the calf of the leg distally. The advancing end of the rod is palpable beneath the skin, and a small incision is made at this point. The segment of the vein containing the rod within its lumen is isolated and opened. The distal portion is ligated. The end of the polyethylene rod is grasped by an assistant, while the surgeon transfixes the upper end of the vein to the stripper by inserting two 00 silk sutures through the wall of the vein and the holes in the trailing end of the stripping rod and securely tying them. Firm, stead traction in the direction of the long axis of the vein is then applied to the advancing end of the rod as the vein is invaginated and avulsed from its subcutaneous bed. Pressure is applied along the course of the removed vein and maintained while the two incisions are closed with interrupted 000 silk sutures. The leg is then wrapped in its entirety with ACE bandages.

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## ADVANTAGES

This instrument has the following advantages over the rigid and malleable metal strippers that are in common use today:

1. It will follow the tortuous course of the vein, thus permitting removal of longer segments than is generally possible with rigid and semirigid stripping rods.

2. Thin-walled, dilated veins are less likely to be perforated with this instrument.

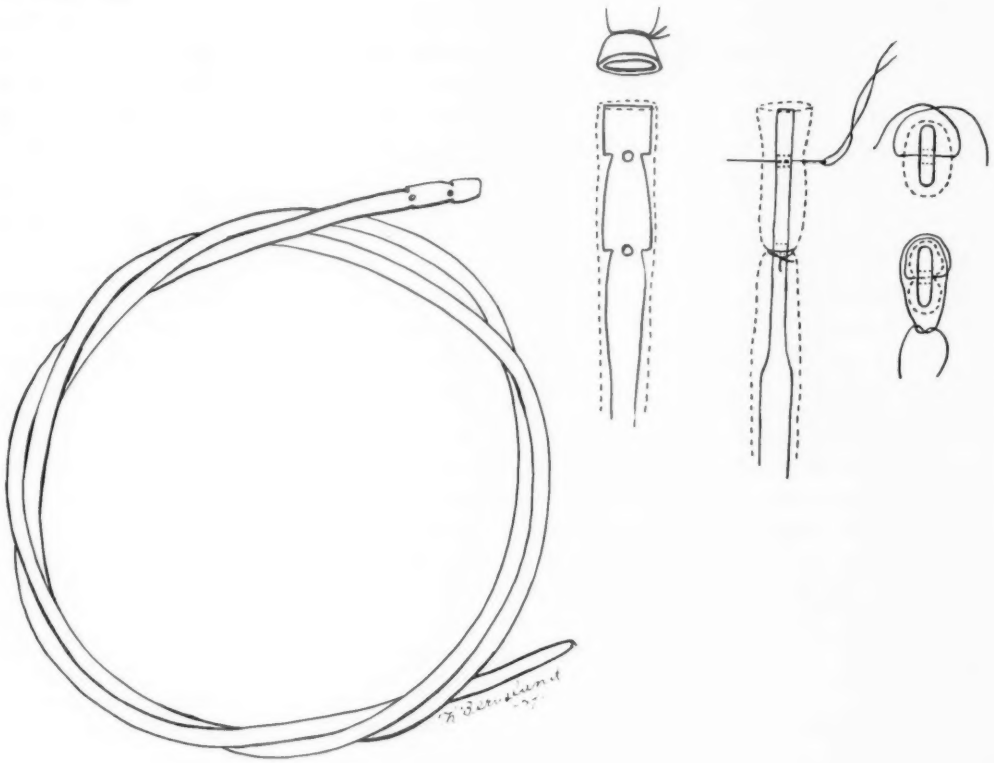

Fig. 1.—A diagrammatic representation of the polyethylene vein stripper. Anterior and lateral views of the proximal end demonstrate the manner in which the vein is transfixed to the rod with silk ligatures.

3. It can be held in a small coil prior to passage into the vein and is not awkward or unwieldy at the operating table.

4. Trauma during removal is minimized by virtue of the polyethylene rod's small diameter.

## SUMMARY

A new vein stripping device made from an extruded polyethylene rod has been presented.

The polyethylene rod possesses certain advantages over metal strippers which are worthy of further clinical trial and evaluation by clinics advocating surgical removal of veins in the treatment of saphenous varices.

The authors wish to express their thanks to the Anchor Plastics Company, 533 Canal St., New York, N. Y., for furnishing us with the extruded polyethylene rod.

# Case Reports

## REGENERATION OF THE LIVER FOLLOWING MASSIVE DESTRUCTION AS A RESULT OF TRAUMA

### Report of a Case and Correlation With Experimental Literature

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MASSIVE destruction of the liver as a result of trauma is a relatively rare occurrence even in those hospitals with active emergency services, the frequency of traumatic rupture of the liver of all degrees being estimated at about one in 1,300 accident admissions.[17, 21] The literature contains several well-documented reports of this intra-abdominal catastrophe and its complications. The controversy between the operative and nonoperative forms of therapy has been adequately explored.[1, 8, 17] However, whereas regeneration of the liver following disease processes has been comprehensively studied both in the human being and in the experimental animal, and whereas numerous studies have been made on regeneration following partial hepatectomy in the laboratory, a careful survey reveals no comment on the eventual fate of this organ following its massive mechanical injury in the human being. This is understandable, for the mortality of these cases varies from 60 to 80 per cent in the first few hours, and the opportunities for exploration in the occasional survivor must indeed be rare. It is of interest, therefore, to report this case of a young, healthy man with destruction of approximately two-thirds of the right lobe of the liver as a result of trauma, who, because of the availability of large quantities of blood, survived for seventy days before coming to post-mortem examination.

#### REPORT OF CASE

F. B., a 25-year-old white man, was admitted to the Post-Graduate Hospital on Aug. 11, 1948.

Nine days prior to admission, while at work, the patient was struck in the region of the right lower chest and flank by a heavy boiler swinging on a crane. This was followed immediately by shock and collapse though without loss of consciousness. He was promptly transferred to a neighboring hospital, where, following intravenous infusions of plasma and whole blood, shock was controlled and the blood pressure stabilized within normal limits. With the return of a normal sensorium he became aware of severe pain and tenderness in the right upper quadrant, and shortly afterward noticed a gradually increasing dyspnea. Flat films of the abdomen taken at this time were reported as negative and red cells were reported in one specimen of urine. Under conservative management there was an apparent, short-lived improvement. On the third day he developed a low-grade fever with temperature swinging daily between 101 and 102° F., and an icteric tinge to the sclerae. The abdomen became increasingly distended, uncontrolled by intragastric suction. There was marked dyspnea and a gradually rising blood pressure which reached a level of 210 systolic. An icteric index taken on the seventh day was reported as 50. Stools were normal in color and urinary output was apparently satisfactory. Nine days after injury, the patient was transferred to the Post-Graduate Hospital.

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Physical examination on admission revealed a well-developed white man in good nutritional condition, markedly dyspneic and appearing acutely ill. He was well oriented though there were transient periods of confusion. The temperature was 101° F., the pulse 120, and respirations were 44. The skin was moderately icteric. There was no peripheral edema. The heart was normal in size with regular rhythm and an apex rate of 120. No murmurs were audible. The blood pressure was 145/98. The lungs were clear throughout but both diaphragms were elevated. The abdomen was markedly distended and tense with an easily demonstrable fluid wave. Acute tenderness was present in the right upper quadrant with an almost complete restriction of abdominal breathing. There was marked tenderness to fist percussion over the right flank and right costovertebral angle.

Laboratory examination revealed an erythrocyte count of 4.5 million with 12 Gm. of hemoglobin and 36,800 leucocytes of which 88 per cent were neutrophiles. The icteric index was 42.4 units; total cholesterol, 115 mg. per cent, esters, 40 mg. per cent; urea nitrogen, 44 mg. per cent; nonprotein nitrogen, 60 mg. per cent; creatinine, 3.3 mg. per cent. The urine had a specific gravity of 1.018 and contained a faint trace of protein. It was otherwise negative. Sedimentation rate was 49 mm. per hour.

A tentative diagnosis was made of rupture of the liver with hemocholeperitoneum, damage to the right kidney with azotemia and hypertension on the basis of a right renal ischemia, and jaundice due to absorption of blood.

*Course in Hospital.*—On the day following admission, the patient was taken to the operating room and, under local anesthesia, 8,000 c.c. of old blood and bile were aspirated from the peritoneal cavity through a small paracostal incision. No exploration was attempted and the wound was closed about two drains. Following this, under a regime of intravenous fluids and blood, there was a slight improvement in the patient's general condition. The mental confusion cleared and, on the nineteenth day postinjury, the blood chemistry had been completely normal, though the blood pressure had risen to 170/100. However, the patient continued markedly dyspneic so that constant oxygen was necessary. Temperature continued septic in type, swinging daily between 99 and 102° F. apparently unaffected by adequate doses of penicillin and sulfonamides. Cultures of the intraperitoneal fluid had revealed no growth, nor had there been any re-accumulation of fluid in the abdomen.

On the twenty-fourth day, because of the continuing fever and dyspnea and lack of general improvement, it was decided to move the patient to the x-ray department for study, since previous portable films had been unsatisfactory. During this procedure, while under constant nasal oxygen, the patient experienced an episode characterized by sudden respiratory arrest, cyanosis, and generalized convulsive movements. Under artificial respiration with oxygen under positive pressure and with intravenous papaverine, Coramine, and caffeine, respirations returned and the patient improved. Roentgenograms at this time revealed a dense consolidation of the entire right pulmonic field. The right diaphragm was markedly elevated with an increased density in the subdiaphragmatic area. The patient was returned to his room, a needle was inserted in the sixth intercostal space in the midaxillary line, and 1,300 c.c. of bile and 200 c.c. of a liver-like paste were aspirated. Because of a previous similar episode occurring on the sixteenth day, and because of a slight corroborative edema of the right leg, it was felt that the most probable explanation of this episode of sudden respiratory arrest was a pulmonary embolus. Reasoning that the danger of a third embolism was greater than the possibility of hemorrhage occurring four weeks after injury, and since the patient's condition contraindicated any operative procedure, he was placed on heparin and Dicumarol. Continued aspirations in the sixth intercostal space were productive of large quantities of bile. It was impossible to determine whether the needle entered the pleural cavity or the subdiaphragmatic space, the former of course postulating a rupture of the diaphragm. The patient's condition was now better than on any previous occasion. Respirations had dropped to 20 to 28 with improved amplitude, and the temperature had fallen to 100° F. On the twenty-sixth day, the prothrombin time was 32. That evening he complained of a sudden sevene pain in the right upper quadrant. The temperature rose sharply to 104.6° F., the pulse rate to 140 and almost imperceptible, and the blood pressure was not obtained. The rapid infusion of 2,000 c.c. of

whole blood together with massive doses of vitamin K resulted in a satisfactory response, the blood pressure rising to 110/70. However, he continued to bleed during the next thirty-six hours and the blood pressure was maintained only by constant transfusion. On the twenty-eighth day, it was decided that operation could no longer be delayed. Accordingly, with large quantities of blood on hand and under light cyclopropane anesthesia, the abdomen was entered through a right paracostal incision and the subphrenic space explored. About 5,000 c.c. of blood clot and pieces of necrotic liver tissue were scooped out of the cavity. There was a tremendous defect in the posterior superior surface of the liver, large enough to accommodate both fists. It was judged that approximately two-thirds of the right lobe had been destroyed. The diaphragm was intact, its dome reaching to the fourth intercostal space. Bleeding from the liver defect was alarming. The defect was lined with large sheets of Gelfoam and about four yards of leg roll packing was packed over this and the end brought out through a counter-incision in the sixth intercostal space, the pleurae being adherent at this point. A Penrose drain was placed down to the right lumbar gutter and the wound closed. Following operation, bleeding was profuse. The blood pressure and red blood count were maintained within reasonable limits only through constant rapid transfusion, so that during the operation and in the forty-eight-hour period following, the patient received 14,000 c.c. of blood with large doses of vitamin K.

On the thirty-first day, the bleeding had stopped, and during the next few days, with daily transfusions of 1,000 c.c. the patient made slow but steady improvement. The packing was gradually removed and was completely out on the forty-first day. The cavity continued to drain large quantities of bile and several pieces of necrotic liver were removed from the cavity. In spite of two other minor episodes of hemorrhage, impovement continued generally, and on the fifty-fourth day, he was permitted out of bed in a chair, and thus gradually began to walk. However, the temperature again became septic in character and on the sixty-third day began a daily swing between 102 and 104° F. Once again the course became downhill and the small gains made in weight and general strength were now more than nullified. Large doses of penicillin, streptomycin, and the sulfonamides were without any apparent effect, and it was decided to explore the cavity for possible abscess formation. On the sixty-eighth day, under cyclopropane anesthesia, portions of the tenth and eleventh ribs were removed, the diaphragm severed, and the walls of the cavity and perinephric area carefully explored. No loculated pus was found. Several fragments of necrotic liver tissue were removed. The presenting portion of the remaining liver was needled and no pus was encountered. Bleeding was profuse. The walls of the huge cavity were lined with Oxycel. Penrose drains were placed in the cavity and the wound partially closed. Hemorrhage following the the procedure was again very great and maintenance of blood pressure required massive transfusions. On October 10, there was a marked drop in urinary output to 130 c.c. and on the following day there was complete anuria. In spite of continuous transfusion, the blood pressure fell, the patient became comatose and died on October 11, seventy days after injury. It is of interest to note that from the time of admission, the patient received a total of 40,000 c.c. of whole blood.

*Post-mortem Findings.*—Autopsy revealed the peritoneum coated by layers of bile-stained fibrin. There were a few fibrinous adhesions between the loops of small intestine. The spleen was enlarged and weighed 420 grams. The microscopic picture was essentially normal. The splenic vein and artery were patent throughout.

The liver weighed 2,700 grams. Approximately one-third of the right lobe remained and measured 17 by 15 by 8 cm. It was the site of a large defect containing 500 c.c. of blood colt. The left lobe appeared hypertrophied to about three times its normal size and measured 26 by 31 by 8 cm. The normally sharp edges were smooth and rounded and the entire lobe had a truncated appearance. The right lobe cut with increased resistance. On section the cut surface had a variegated appearance. In some areas the lobular architecture appeared intact. The central veins, however, were congested. Wedge-shaped areas were seen in which the lobular architecture could not be distinguished. The left lobe cut with normal resistance. On section the cut surface bulged and the lobular architecture appeared intact. The individual lobules appeared larger than normal.

Microscopically, sections through the right lobe revealed the lobular architecture to be intact. In a few areas the nuclei of the liver cells could not be seen and the sinuses in these areas were markedly distended with blood. Some areas revealed the liver cells undergoing necrosis. The portal spaces showed some slight degenerative changes.

Sections through the left lobe revealed an intact lobular architecture. The nuclei of the liver cells varied to some degree. Portal areas were not remarkable. The portal vein was patent throughout and its intima smooth. The gall bladder and entire extrahepatic biliary system were normal.

The right kidney weighed 100 grams. The right renal artery was completely occluded by a gray friable clot adherent to the intima. Microscopically the entire kidney was the seat of an ischemic infarct. The left kidney was enlarged to 300 grams and a microscopic examination showed a glomerular hypertrophy.

Both lungs showed a basilar atelectasis and a generalized pulmonary edema.

## DISCUSSION

Since its original suggestion by Cruvelhier,[3] regeneration following injury has been established as one of the outstanding characteristics of liver tissue, though doubt has existed as to its degree and method. As pointed out by Fishback,[4] the term regeneration is somewhat ambivalent in describing this process as it occurs in the liver, for in the experimental animal growth following partial hepatectomy does not occur at the level of the cut surface, nor do new lobes take the place of those removed, such as the response which follows the removal of appendages in the lower animal forms. There is rather a hyperplasia within the remaining lobes with a definite restoration of lobules and of hepatic cells resulting from a generalized mitotic activity, so that the process does not fulfill the biologic requirements of true regeneration.[4, 5] Fishback[4] found the picture analagous to that seen in the embryonic development of the liver, the chief factor being the intense and rapid multiplication of hepatic cells at the periphery of the lobules with the bile ducts sending forth buds of proliferating cells. The lobules do not hypertrophy but undergo a hyperplastic budding at their periphery so similar in size and shape as to be indistinguishable from the old ones. Thus, when three-fourths of the liver has been removed in the animal, the restorative process is initiated within the remaining lobes in the first twenty-four hours, with the liver attaining its orginal size in six to eight weeks in the dog[4] and in ten to fourteen days in the rat.[10]

The usual term applied to the restorative process when occurring in other organs is a compensatory or work hypertrophy. Whereas it would seem probable that partial loss of an organ with such a multitude of functions as the liver has would create a physiologic need, such apparently has not been the case. In none of these surviving animals has there been any indication that normal physiology had been disturbed.[5, 7, 10, 11, 16] After ligating branches of the portal vein to the main liver in the rabbit, Rous and Larimore[16] found that the portion of the liver deprived of portal blood underwent complete atrophy, while the portion receiving portal blood hypertrophied to a degree equal to the original liver mass. This was the first evidence that restoration of the liver following partial removal is not a work hypertrophy. Mann and coworkers[10, 11] found that restoration was retarded or absent in a liver partially

deprived of portal blood due to the creation of an Eck fistula. They showed further that partial hepatectomy done on cirrhotic livers resulting from previous ligation of the common bile duct was followed by a marked decrease in the degree of regeneration. Similar observations were made by Stephenson[18] when partial ligation of the portal vein was coincident with partial hepatectomy. It would seem that any attempt to restrict the restorative power of the liver is dependent upon a decreased portal blood flow, and that any injury to the liver such as cirrhosis, which restricts the portal circulation, will cause a further decrease in this characteristic. Restoration, then, is dependent upon an intact portal channel and apparently occurs in order to establish an adequate portal pathway. However, there is no final evidence to show that the stimulus for restoration does not lie within some element of the portal blood itself.

In correlating the regeneration of the liver occurring in this report with that of the experimental literature, no comparison can be drawn as to the actual morphology of the restorative process. For the description of its day-to-day development, so thoroughly documented in the experimental animal, is manifestly impossible in the human being. There is, however, a striking parallel in their final restoration, so that Mann's[10] description of the restored liver in the rat is an accurate picture here.

"The gross appearance of the restored liver is very characteristic and can easily be recognized. The edges of the lobes are rounded as compared to the knife-like edges of the lobes of the normal organ. The body of the lobe becomes dome-shaped and the lobe as a whole tends to become spherical."

Here again replacement of tissue did not occur at the site of the fractured surface. No new lobes were formed. There was rather a remarkable hypertrophy of the left lobe so that the entire weight of the liver, 2,700 grams, considerably more than equaled the average weight of the normal liver, 1,200 to 1,500 grams. Normally, the left lobe occupies about one-half the volume of the right lobe and about one-third of the entire volume of the liver. The conditions here were very nearly reversed. The left lobe with an approximate volume of 3,328 c.c. occupied nearly twice the volume of the right lobe, 2,040 c.c., and formed three-fifths of the entire liver. It would seem that the left lobe had hypertrophied to more than three times its normal size.

Microscopically, beyond some degree of variation in the nuclei of the liver cells in the left lobe, the picture was completely normal. The lobular architecture was intact and the portal areas not remarkable. Mann[10] pointed out that it is usually impossible to differentiate restored liver tissue from the normal microscopically, after the completion of restoration. Since restoration in the dog is complete after six to eight weeks, it may be assumed that restoration here was complete after seventy days.

A report of this patient, we believe, is of some interest, not only in indicating the possible fate of the liver following its partial traumatic destruction, but also its fate following partial hepatectomy for malignant disease.

SUMMARY

1. A case of regeneration of the liver in the human being following massive mechanical destruction is reported.

2. The experimental literature is reviewed.

3. Regeneration of the liver in the human being following trauma parallels the regeneration of the liver occurring in the experimental animal following partial hepatectomy.

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# TUBERCULOUS SUBDIAPHRAGMATIC ABSCESS WITH PULMONARY MANIFESTATIONS

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THE occurrence of a subdiaphragmatic abscess in itself is rather common, but a tuberculous subdiaphragmatic abscess, in the absence of a coexisting tuberculous process in the abdomen, presenting thoracic complications is rare. Our recent encounter with such a case prompts this report.

## PATHWAYS OF INFECTION

Hochberg[3] stated that the subphrenic spaces may become infected in a number of ways, the usual ones being (1) directly from the peritoneum or contiguous organs as the gall bladder, stomach, duodenum, kidney, spleen, pancreas, and so forth; (2) by direct extension from an appendical infection or a pelvic abscess; (3) by rupture of an hepatic abscess or a thoracic empyema into the subphrenic space and by extension from an osteomyelitis of a rib; (4) retrograde lymphatic flow from a pulmonary abscess or thoracic empyema; (5) hematogenous spread from an osteomyelitis, septicemia, or furunculosis; and (6) by direct implantation by injury to an anatomically related organ.

Ochsner and DeBakey[4] in a collected series found that the etiology could be traced to an intra-abdominal infection in 84 per cent of 3,608 cases. The extension of a thoracic infection into the subphrenic region was responsible for only about 2.5 per cent of the cases.

While a tuberculous subphrenic infection may occur in association with a tuberculous peritonitis, a tuberculous subdiaphragmatic abscess from other causes is unusual. Gill and Mann[2] reported a case complicating primary splenic tuberculosis. Piquand[5] in 900 collected cases found 23 due to tuberculosis complicating diseases of the gall bladder, liver, kidney, and lung. None of the 3,608 cases analyzed by Ochsner and DeBakey[4] were tuberculous. One in 80 personal cases observed by Clagett and Tinney[1] was due to tuberculosis. None of the reported cases of tuberculous subdiaphragmatic abscess ended in recovery.

## THORACIC COMPLICATIONS

The thoracic complications of a subdiaphragmatic abscess constitute the greatest danger. Of the 3,608 cases previously referred to by Ochsner and DeBakey,[4] the most important thoracic complications in the order of frequency were pleurisy, perforation of the diaphragm, empyema, and bronchial fistula. The incidence of bronchial fistula was 10.5 per cent. In 75 cases there was a reported mortality of 50 per cent in those with thoracic complications and mortality of only 16.3 per cent in those without complications. Clagett and Tinney[1] reported a 65 per cent incidence of thoracic complications in 80 patients seen personally. A bronchial fistula was present in 40 per cent. The

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mortality in the group with pulmonary complications was 44 per cent and 32 per cent in those without pulmonary complications. The mortality was 50 per cent in those with a bronchial fistula and 29 per cent in those without a bronchial fistula.

## CASE REPORT

A case with a tuberculous subdiaphragmatic abscess with a phrenobronchial fistula constituting a source of positive sputum is presented.

A 49-year-old white woman (Case No. 8363) entered the Franklin County Tuberculosis Hospital, Columbus, Ohio, March 28, 1947, complaining of productive cough and hemoptysis.

In the past history, the patient stated that five years previously she had had an operation for perforated peptic ulcer and at that time a gastroenterostomy was performed. Six months after the gastroenterostomy the patient underwent another operation for symptoms of small bowel obstruction. At this time a subhepatic abscess was found and was drained after relieving the obstruction. The wound drained for about six weeks and finally closed, the patient remaining asymptomatic except for occasional attacks of mild epigastric pain after eating, relieved by antacids.

In February, 1946, the patient developed pain in the anterior right part of the chest, which was followed by attacks of chills and fever. A cough productive of thick sputum with hemoptysis then developed. A chest x-ray examination in July, 1946, by her family physician was reported to have shown a cavity on the right side in the upper third. The sputum examinations were negative for acid-fast bacilli and supposedly a diagnosis of cystic disease of the lung was made. The symptoms continued and in January, 1947, another chest x-ray view revealed progression of the disease. At this time the sputum was positive and she was referred to the hospital for therapy.

Upon admission, physical examination revealed a well-developed, well-nourished, white woman, 49 years of age, who did not appear ill. The temperature was 99° F., pulse 92, respiration 20. The blood pressure was 124 systolic and 76 diastolic. Examination of the chest revealed a lag in respiration on the right side; slight impairment to percussion, increased breath sounds, and moderately coarse râles over the upper anterior right part of the chest. A right rectus scar on the abdomen was present; no other significant findings were found. The vital capacity was 1,800 c.c.

Laboratory examination revealed the sputum to be positive for tubercle bacilli. Sedimentation rate was 0.64 mm. per minute. The hematocrit was 28.08. The blood count revealed a hemoglobin of 8 Gm.; red blood cells, 3,400,000; white blood cells, 10,500, with a differential of 68 per cent segmented neutrophils, 3 per cent nonsegmented neutrophils, 17 per cent lymphocytes, 1 per cent monocytes, 11 per cent eosinophils. Urinalysis was negative, serology negative; the blood type O, Rh negative. The old tuberculin skin test was positive at a strength of 1:10,000 and the histoplasmin and coccidioidin skin tests were negative.

A chest roentgenogram showed infiltration in the right upper lobe extending down to the level of the third anterior rib. There was a small area of decreased density about 1 cm. in diameter in the upper lobe.

Due to occasional attacks of epigastric pain after eating, it was decided to investigate the gastrointestinal tract. Barium studies revealed no evidence of pathology in the gastrointestinal tract. A cholecystogram revealed a normal functioning gall bladder without evidence of stones. In the flat film of the abdomen there was an area of increased density in the upper right abdomen and since physical examination and barium studies of the gastrointestinal tract were negative, retrograde urograms were carried out. These revealed the right kidney to be displaced downward and the upper pole not accurately identified due to the presence of a curved band of increased density superimposed on the upper pole of the right kidney. Kidney function tests were also normal. All examinations of the urine were negative

including guinea pig inoculation for tubercle bacilli. It was finally decided that this downward displacement of the right kidney was probably due to an area of increased density as shown by x-ray films; it was probably formed by adhesions and scar tissue following the subhepatic abscess five years previously.

Preliminary bronchoscopy was negative; bronchography revealed no evidence of bronchiectasis or bronchial stenosis; all segments filled well. The electrocardiogram was normal.

All examinations having been completed, the patient was started on right therapeutic pneumothorax; this proved unsatisfactory due to apical adhesions, and the lung was allowed to re-expand. A thoracoplasty was decided.

A right, two-stage seven-rib thoracoplasty was completed on Oct. 7, 1947, and the patient made an uneventful recovery; however, about three weeks after this she started to expectorate blood. She continued to raise about one to two ounces of blood a day. Since she had had an excellent collapse from the thoracoplasty and since complete blood studies failed to reveal any evidence of a possible blood dyscrasia it was decided that the bleeding might be coming from a diseased area or possibly from a cavity which had not been demonstrated. Esophagoscopy was negative; on numerous occasions blood was seen to be coming from the right common bronchus during bronchoscopy. It was finally decided that a lobectomy should be performed to control the persistent hemoptysis.

The patient received streptomycin, 2 Gm. daily for seven days, and penicillin, 150,000 daily for two days preoperatively; on Nov. 25, 1947, a right upper lobectomy was performed. During operation the only diseased area found was in the upper lobe and since the patient had a previous thoracoplasty the remaining lung was not mobilized following the resection. Postoperatively the streptomycin and penicillin were continued for two weeks; she made a satisfactory recovery. The surgical specimen revealed several calcified deposits in association with one sizable bronchus; however, no evidence was encountered to prove that these areas were in the process of ulcerating into the bronchi or that they might serve as a source of bleeding. Several solid caseous lesions up to 5 mm. in diameter were found and several of the bronchi revealed the presence of tubercles. The final diagnosis was chronic fibrocaseous pulmonary tuberculosis, and tuberculous bronchitis.

The patient was completely asymptomatic for one month after the lobectomy, at which time she expectorated about two ounces of blood. Prior to this, sputum examinations had become negative, but repeat sputum examinations after the hemoptysis were again positive. She again developed a productive cough and the sputum was purulent and bloody and averaged one to three ounces a day.

Chest x-ray examination revealed no new areas of disease. A repeat bronchogram failed to demonstrate any abnormality, and bronchoscopy revealed bloody purulent sputum coming from the right lower lobe. A diagnostic thoracentesis failed to demonstrate any fluid. It was decided that the patient should have an exploratory thoracotomy, in an attempt to locate the source of bloody purulent sputum which was positive for acid-fast bacilli.

The patient again was placed on a preoperative course of streptomycin and penicillin, and on March 2, 1948, a right exploratory thoracotomy was performed. There was no intrapleural fluid and the lung felt normal to palpation. The middle and lower lobes were completely mobilized and in so doing an area was encountered in the medial, inferior, posterior portion of the lower lobe which was densely adherent to the diaphragm. This area was separated by sharp dissection, and a fistulous tract was encountered from which poured purulent, bloody material similar to the sputum the patient had been expectorating. This material came from the distal portion of the fistulous tract, and when the tract was followed distally, it was found to lead through the diaphragm into an antrum approximately 2 by 3 cm. This was completely unroofed. The lung appeared normal with the exception of the fistulous tract; this was removed. It was decided to drain the abscess through the thorax, packing the antrum with gauze to be removed later. Postoperatively the streptomycin and penicillin were continued for two weeks and the patient made a satisfactory recovery. Culture of the drainage from the abscess cavity revealed tubercle bacilli and gram-positive cocci.

A diagnosis of a tuberculous abscess with a phrenobronchial fistula was made.

The gauze packing was gradually removed over a period of two weeks at which time the lung was fairly well re-expanded, the empyema space being quite small, and the abscess cavity below the diaphragm could no longer be palpated or demonstrated with lipiodol. At the end of six weeks the empyema space held only 50 c.c. of saline solution, and there was only a small amount of drainage from the empyema. The patient was otherwise asymptomatic and all sputum examinations were negative by five-day concentrates and cultures.

The patient was started on graduated exercise and was progressing quite satisfactorily. On May 8, 1948, five months later, she complained of a headache, nausea, and loss of appetite. The following day she developed projectile type of vomiting. All physical examinations were negative; there was no elevation in temperature and the patient stated she felt well between attacks of vomiting. That evening she lapsed into a coma and developed rigidity of the neck but no other signs of a localized lesion. A spinal tap was performed revealing an initial pressure of 21 mm. mercury. The spinal fluid was clear. Examination revealed 800 cells per cubic centimeter, 100 per cent being lymphocytes. The chlorides were 826 mg. per cent, sugar 16 mg. per cent, and proteins 441 mg. per cent.

The patient remained in coma, rigidity of the neck persisted, and a flaccid paralysis of all extremities developed. The following day, on May 10, 1948, the patient died.

An autopsy was performed and the essential findings were as follows.* There was a small empyema cavity in the base of the right thorax which was dependently drained. There was no evidence of an extension below the level of the diaphragm. Multiple section of both lungs showed no evidence of caseation, calcification, or cavitation. Very dense adhesions were encountered in the right upper quadrant of the abdominal cavity. There was no increase in abdominal fluid and no exudate present. Extremely dense scar tissue was present between the liver and diaphragm to the right of the falciform ligament. Multiple sections through the lower lobe of the right lung, of the diaphragm, and the right lobe of the liver revealed nothing except extremely dense scar tissue in and beneath the diaphragm and at times on the upper surface of the diaphragm. There was a 5 mm. ulceration on the lesser curvature of the stomach at the pylorus. This was adherent to the head of the pancreas and showed no evidence of perforation at this time. Examination of the brain revealed flattening of the convolutions and obliteration of the sulci on removal of the dura mater. There was an increase in subarachnoid fluid and congestion of the meningeal vessels. On removal of the brain, inspection of its base revealed a thick granular gray exudate on the anterior surface of the brain stem and cerebellum and on the undersurface of the cerebral hemispheres. The exudate was abundant in the area of the optic chiasma. Careful inspection of the undersurface of the optic nerve revealed multiple pale granular lesions thought to be tubercles. Multiple section through the left cerebral hemisphere showed the left lateral ventricle to be filled with a thick sanguinopurulent exudate. The ependyma of the ventricle was hemorrhagic. In an area immediately above the brain stem and on the upper surface of the left lateral ventricle a ragged cavity about 5 mm. in diameter was found. The right lateral ventricle appeared normal; however, the fourth ventricle contained a thick purulent exudate. Microscopic examination revealed no evidence of tuberculosis in the brain, the diagnosis being a metastatic brain abscess with purulent meningitis, nontuberculous.

## COMMENT

1. A brief review of the etiology of subdiaphragmatic abscess and the incidence of pulmonary complications is presented.

2. A case is presented in which the source of a positive sputum following a pulmonary resection for tuberculosis was found to be due to a tuberculous infection superimposed on a chronic subdiaphragmatic abscess with a phrenobronchial fistula.

*Autopsy performed by Dr. H. B. Davidson, Pathologist for the F.C.T.H.

3. A diagnosis of a tuberculous subdiaphragmatic abscess with a phrenobronchial fistula was made at the time of operation. The modus operandi of this infection is a matter of conjecture. Although no x-ray films were present at the time of the abdominal surgery, it may be assumed that a pulmonary lesion was present and that gastric contents contained tubercle bacilli, producing a mixed infection of the subphrenic space following the gastric surgery. No clinical symptoms were manifest until development of the phrenobronchial fistula shortly before admission to the hospital.

4. Autopsy findings indicated that there was no longer any evidence of pulmonary tuberculosis following pulmonary resection. There was apparently a cure of the tuberculous subdiaphragmatic abscess which by necessity had been drained transpleurally. Death, occurring sixty-nine days following the last operation, was due to a metastatic brain abscess with rupture into the lateral ventricle and an overwhelming purulent meningitis, nontuberculous.

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# SOLITARY HEMANGIOMA OF SMALL INTESTINE

## Abstract of Literature and Report of a Case

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HEMANGIOMAS of the intestinal tract are comparatively rare and are seldom diagnosed correctly except by operation or autopsy. We are impressed by the diagnostic possibilities when a patient complains of melena associated with anemia, weakness, and abdominal cramps, in the absence of demonstrable x-ray evidence of disease. The rarity of this lesion warrants the reporting of all cases.

Various pathologic classifications have been made of hemangiomas of the gastrointestinal tract. Kaijser[1] divided hemangiomas into four types and considers them all to be congenital in origin:

1. Multiple phlebectasias. These are not infrequent.

2. Cavernous hemangioma occurring in two different forms. One is found in the wall of the intestine with no well-marked delineation of the borders of the mass. The other is a sharply delimited, frequently polypoid tumor, usually found in the colon. All of these growths with their widely dilated venous loops frequently contain phleboliths which, if calcified, may give roentgenologic findings of diagnostic significance.

3. Simple or capillary hemangioma. From these may develop large cell-rich tumors which represent a transition of the hemangioendotheliomas.

4. Angiomatosis. This condition appears under different forms, one of which is known as Rendu-Osler-Weber disease or telangiectasia hemorrhagica hereditaria. It manifests the most variable characteristics. Frequently the microscopic picture of the tumor suggests malignancy, such as a true angiosarcoma, but it is always benign. As a rule this type of tumor of the intestine is accompanied by hemangiomas and warty growths of various sorts on the superficial cutaneous surfaces of the body.

Moore[2] further described benign tumors of the small intestine as spherical, solitary, or multiple, and submucosal, intramural, or subserosal. The comparatively small number of reported cases indicates the rarity of this lesion. Ehrlich and Hunter[3] reported that the Army Institute of Pathology examined 813 tumors of the gastrointestinal tract arising in army personnel between the ages of 18 and 38 years in a four-year period from 1941 to 1945. One case of hemangioma was found with multiple lesions in the ileum. One hemangiopericytoma of the stomach was also found.

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Moore[2] found the commonest sites for small bowel tumors to be in the duodenum and ileum. In the order of frequency, he listed adenoma, leiomyoma, fibroma, lipoma, hemangioma, and neurogenic fibroma. Merchant[4] listed the frequency as lipoma, 6; fibroma, 4; adenoma, 3; adenomatous papilloma, 3; hemangioma, 3; carcinoid, 2; fibroadenoma, 1; fibromyxoma, 1; and lymphoma, 1; from a histologic examination of 24 tumors of the small intestine found among 50,775 surgical specimens and 7,340 autopsies.

In the 20 cases of vascular tumors of the intestine summarized by Brown,[5] 8 were multiple lesions and 12 single lesions. Eight of the 12 single lesions were located in the small intestine.

Lichenstein and Dutra[6] in 1943 summarized 116 previously reported tumors of the small intestine, of which 7 were angiomas. Three of these were in the duodenum, 2 in the jejunum, 1 in the ileum, and 1 was unspecified.

Polayes and Nevins[7] in 1945 reported a case of hemangioma and stated that a review of the literature revealed 93 other reported cases of the gastrointestinal tract. Since then, Packard,[8] Ehrlich and Hunter,[3] Smith, Good, and Gray (2 cases),[9] Hanno and Mensh,[10] and Browne and McHardy,[11] with their case reports, have brought the total to 100. At least 5 of these, including the cases of Christopher[16] and Kortzeborn[17] were similar to our case.

Histologically, hemangiomas are neoplasms made up of blood vessels which Moore[2] believes have arisen from remnants of fetal tissue misplaced or disordered in development. Combinations of solid tumor cell masses and open vessels occur.

Ewing[12] stated that, "Not being composed of a simple tissue, tumors of vessels must be organoid in character. The growth of vessels is markedly influenced by the element of mechanical pressure of the circulation, which is absent in other tumors. The physiology of vessels necessitates special standards in the interpretation of tumor processes, and this peculiarity has led to much difference of opinion as to what constitutes an angioma."

Watson and McCarthy[13] in their report of 1,056 cases of blood and lymph vessel tumors stated that in all but the racemose type the tumor growth generally stops with full body growth and that 73 per cent of patients presented evidence of tumors at birth. Females were more frequently affected than males in the ratio of about 65 to 35. The sexes were about equally represented in cases of hemangioma of the gastrointestinal tract. No cases of metastasis have been reported of hemangioma of the gastrointestinal tract, but this possibility is discussed by Ewing.[12]

In Brown's[5] series of 20 cases of intestinal hemangiomas, 7 gave no symptoms, 6 suffered from gastric or intestinal hemorrhage, 1 from nausea and epigastric distress with vomiting after eating, 1 from chronic intestinal obstruction, 4 from acute intestinal obstruction, and in 1 case the symptoms were not given.

A review of case reports indicates that melena, anemia, and weakness are the outstanding symptoms. Abdominal pains simulating appendicitis are sometimes encountered, and appendectomy was done in the case herein reported

and in others. Cramping abdominal pains and audible intestinal gurgling indicate partial obstruction and are common complaints. Vomiting and an abdominal mass may occur if there is obstruction. It is of interest that in several cases of gastrointestinal hemangioma there were also hemangiomas of the skin.

Smith, Good, and Gray[9] reported 35 tumors of the small bowel, 2 of which were hemangiomas. There was loss of blood in 28. In patients with an ulcer type of distress, a demonstrable deformity of the duodenal bulb and a history of melena, two lesions may be present, and these authors suggest that it is well to search for other lesions at the time of operation, even if an ulcer is found.

The case reported by Hanno and Mensh[10] illustrates the danger in assuming that high intestinal bleeding is due to ulcer. Their patient, a man 53 years of age, died of hemorrhage from a hemangioma of the jejunum. He had suffered from intermittent melena for fourteen years, and gastroenterostomy was performed on suspicion of peptic ulcer, although no ulcer was actually found on x-ray examination or at operation.

Lichtman[14] in 1946 reported a series of 49 cases of primary carcinoma of the duodenum and stated that the Mayo Clinic records indicated that there were 266 patients with bleeding from peptic ulcers or carcinoma for every one with a bleeding small bowel tumor in a three-year period.

In Weber's discussion of Lichtman's report on the roentgenologic diagnosis of tumors of the duodenum, he mentioned the fact that standard roentgenologic examination of the gastrointestinal tract usually includes only the first part of the duodenum. When there is unexplained anemia from chronic loss of blood, the roentgenologist should examine the entire duodenum if he has been given such diagnostic clues from the referring physician.

In both cases reported by Kaijser,[1] there was a deposition of calcium in the cavernous spaces forming phleboliths, which were roentgenologically demonstrable. He noted that phleboliths are often found in the small pelvis, but practically never in the other regions of the abdominal cavity.

Unexplained melena after proper study warrants exploration as undue delay may result in a fatal outcome from hemorrhage. Frequently, an aid in locating the lesion is a pulsating artery leading into the mass. Others have described such an artery, and one was seen by us. Resection is the treatment of choice. If widespread distribution of multiple lesions contraindicates resection, irradiation can be tried, noting at the time of laparotomy the areas of probable hemorrhage as an aid to the roentgenologist. In one of Kaijser's[1] cases, a large cavernous hemangioma of the stomach near the lesser curvature was successfully treated by radiation. Cauterization has been used in some cases, usually with only temporary relief. Bancroft[15] injected a coagulating substance in one case.

## CASE REPORTS

W. H. E., Jr., aged 26 years, was first seen by us on Jan. 7, 1947, complaining of a painful amputation stump, abdominal cramps, and anemia. The onset of illness dated back to early 1940 when he had had an attack of cramping abdominal pain which was diagnosed

as appendicitis and an appendectomy was done. With the pain, he had the first hemorrhage from the bowel, and this had recurred about every six months for the past seven years. The bleeding persisted for several days to weeks and produce a marked anemia, which had necessitated a total of some forty-eight blood transfusions. Over this seven-year period, he had cramping pain in the lower abdomen and around the umbilicus, usually occurring about one-half hour after meals. Food taking usually induced the pain and never relieved it. The pain was often associated with nausea and vomiting, especially after breakfast, and lasted two to three hours. Morphine was sometimes necessary for relief. He never vomited blood but often had tarry stools. Bowels were normal except during the bleeding, and he had occasional attacks of substernal and epigastric burning distress.

In October, 1946, the patient had a severe hemorrhage and was given a transfusion. Following one of the transfusions, he developed gangrene of the right arm and hand, necessitating an amputation below the elbow. In addition to the appendectomy, a right inguinal hernia was repaired in 1940 with an attempt to bring down an undescended testicle.

Physical examination revealed tenderness in the lower abdomen, especially on the right side, but there was no mass, no rigidity, and no rebound tenderness. Appendectomy and right inguinal herniorrhaphy scars were seen, and the right upper forearm amputation stump was incompletely healed. Physical examination was otherwise negative, and no skin hemangiomas were found.

The Ewald test meal had 48 units of free HCl and 72 units of combined. Benzidine tests for occult blood in the stool showed strongly positive, but the stool was yellow to brown in color. On Jan. 8, 1947, the total protein was 7.10 Gm. with a red count of 2,980,000, a white count of 10,000, and a hemoglobin of 7.5 Gm. There was hypochromia and anisocytosis 2 and microcytes 3. Barium meal and roentgenologic studies of the gastrointestinal tract were negative, and the patient was discharged with a diagnosis of probable duodenal ulcer and neuroma of the amputation stump.

On May 19, 1947, the patient was readmitted with the same complaints and recurrent bleeding from the intestinal tract. Gastrointestinal x-ray series again showed no abnormalities. Proctoscopic examination was not helpful. The stools were brown with a 4+ benzidine test, red count was 3,240,000, white count 12,500, and hemoglobin 8.3 Gm. There was an anisocytosis and the differential count showed 76 polymorphonuclear neutrophiles, 13 lymphocytes, 9 eosinophiles, and 2 myelocytes. The patient was prepared for laparotomy with a preoperative diagnosis of a probable bleeding Meckel's diverticulum.

Exploration revealed a pulsating constricted area three inches long about one-third of the way down the small bowel. The proximal portion of this area was somewhat dilated as compared with the distal portion past the central constriction. The whole area was hyperemic, purple-red, with numerous fine serosal capillaries, and in the mesentery were dilated veins forming a fan-shaped area extending from the root of the mesentery to the lesion. This portion of the mesentery as well as the segment of the intestine visibly pulsated synchronously with the aortic pulsations. There were small firm lymph glands scattered throughout the mesentery of the small bowel. No other abnormalities were found in the gastrointestinal tract. The spleen was enlarged and firm. The lesion was resected and an open method end-to-end anastomosis was done.

The patient made an uneventful recovery and was discharged ten days following surgery with no abdominal cramps and eating well. In a communication some two years later, he stated that he was entirely free of abdominal complaints, was gaining weight, and had returned to work as a chauffeur.

*Pathologic Report.*—The specimen consisted of a segment of small intestine 11.5 cm. (4½ inches) long with attached segment of mesentery. After fixation, the lumen measured 2.5 cm. in diameter at the proximal end of the segment and 1.8 to 2.0 cm. at the distal end. At approximately the center of the specimen, the lumen was constricted to a diameter of 8 cm. This constricted area occupied the proximal portion of a hyperemic zone of serosa 5 cm. long which was red-brown and granular. The serosa elsewhere was gray, smooth, and glistening. The mesentery was moderately obese and up to 1 cm. in thickness 2.5 cm. from

the bowel. It contained dilated veins and two prominent arteries 3 mm. in diameter. Extending from the mesentery over the serosal surface of the bowel were many fine branching and anastomosing blood vessels. These become so numerous in the hyperemic zone that the individual vessels were identifiable only on magnification. When sectioned lengthwise, the bowel wall was found to be thinner (1 mm.) in the proximal end than in the distal (2 mm.). The rugae encircled the lumen but were definitely more elevated and packed closer in the distal end, which was less dilated than the proximal. At the constricted area, the bowel wall was 3 mm. in thickness on the antimesenteric side. Starting at this area and extending distally for 3 cm. the mucosa lost its normal pattern of rugae and became a granular irregular

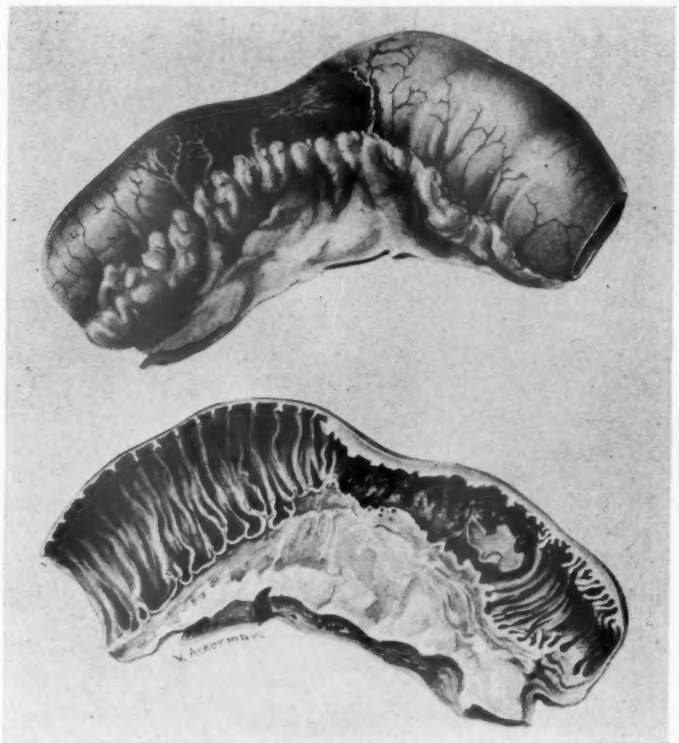

Fig. 1.—Gross specimen (drawing). *Upper figure* illustrates external surface with prominent serosal blood vessels. *Lower figure* shows constriction of lumen, thickening of bowel wall, mucosal ulcer, and prominent mesenteric vessels.

purple-red membrane 2 to 3 mm. thick. Near the distal end of this area was an irregular ulcer with a gray, fairly smooth base measuring 1.2 cm. in the long axis of the bowel and 4 to 6 mm. in width. This ulcer was on the side of the bowel wall and did not extend to the mesenteric aspect of the lumen. Immediately distal to the ulcer, the granular appearance of the mucosa disappeared and the rugal pattern was again visible (Fig. 1).

Microscopic sections revealed the bowel wall altered by the presence of large numbers of various sized spaces filled with blood (Fig. 2). These were most numerous in the muscular coats where they occupied up to one-half of the field. The smaller capillaries consisted only of a single layer of endothelial cells. Most of the larger ones had a similar wall, but occasionally an additional thin layer of fibrous tissue was seen surrounding the endothelial lining. Fine branching vessels could be seen extending between larger blood-filled cavities. Large vessels were prominent in the subserosa. The submucosal layer was strikingly free of capillaries as compared with the muscularis and the mucosa. In the latter, the vessels were smaller but extremely numerous and extended to the inner edge of the mucosa. Much of the mucosa had ulcerated and was represented by very loose areolar tissue showing a

marked inflammatory cell reaction. Plasma cells, eosinophiles, lymphocytes, and leucocytes were seen infiltrating all layers of the bowel wall. The latter were most numerous in the mucosal layers where ulcerations covered by a pyogenic membrane and small masses of necrotic tissue obliterated the normal architecture.

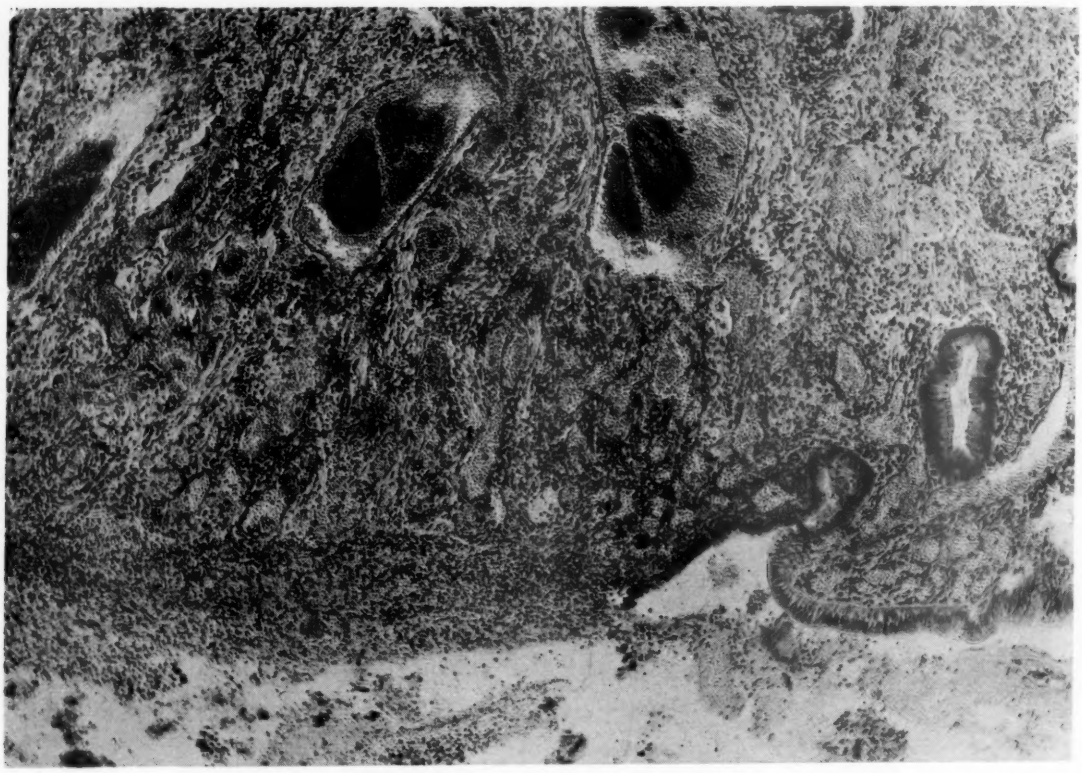

Fig. 2.—Thin-walled blood vessels of various sizes in hemangioma of small intestine. Capillaries extend to ulcerated surface of mucosa.

## CONCLUSIONS

Hemangioma of the intestinal tract is to be considered in patients with recurring episodes of melena, especially when a history of cramping abdominal pain is present. In the jejunum and ileum, these tumors usually are not demonstrable by x-ray studies. Earlier surgical exploration is advisable in such cases.

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# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## V. THE CRUSH SYNDROME IN BATTLE CASUALTIES

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IN the preceding papers of this series[1-4] examples of the crush syndrome have been mentioned, often with little or no distinction from the common battle casualties. This group of cases, however, presents certain distinctive features which require separate consideration. Moreover, although cases were reported in the German literature among casualties of World War I, and although Bywaters[5] and others[6, 7] have done careful clinical and biochemical studies of many civilian casualties during the Battle of Britian, few thoroughly studied cases have been recorded among the battle casualties of World War II.

In this paper the clinical, physiological, biochemical, and pathological features will be presented and the results of treatment discussed on the basis of nine cases, five of which were fatal (Table I). All of the patients were crushed within stone houses typical of the Italian countryside. (It is perhaps not a coincidence that the first known description of the syndrome came from Italy in 1908 as a report of casualties of the earthquake at Messina.) Five of the buildings in which the injuries occurred, one of them housing a medical collecting company, were struck by artillery shells. Two of the casualties resulted when a demolition charge exploded, and the remaining two were incurred when a house about 200 yards from our laboratory was struck at dawn by a bomb from a German raider. It consequently was possible to observe the patients virtually from the moment of release from the rubble in which they were partially buried.

### CLINICAL FEATURES

The clinical features of crush syndrome can be divided into two categories: primary and secondary. The primary features, comprising the direct effects of crushing injury, were common to all nine men. The secondary features, seen only in the five fatal cases, were the usual signs and symptoms of posttraumatic renal insufficiency.

*Primary Phase.—*

*Shock:* Shock, as judged by the usual clinical criteria, was not characteristic of the majority of our patients with the crush syndrome and was never seen in patients observed within ten hours of release from the compressing agents. One patient (Case 70*), for instance, looked so well when examined

*Our case numbers have been retained in this paper because of their possible later interest if this source material is published by The Surgeon General.

TABLE I. DATA CONCERNING NINE PATIENTS WITH CRUSH SYNDROME

| CASE NUMBER | AGE OF PATIENT (YR.) | DURATION OF CRUSH (HR.) | HOURS FROM RELEASE OF CRUSH TO ARRIVAL AT HOSPITAL | HOURS FROM RELEASE OF CRUSH TO ADMINISTRATION OF FIRST I. V. FLUID | PARTS AFFECTED | OPERATION | HOURS FROM RELEASE OF CRUSH TO OPERATION | OUTCOME |
|---|---|---|---|---|---|---|---|---|
| 56 | 25 | 6 | 6 | <6 | Left shoulder, pelvis, both hips | None | | Lived |
| 73 | 34 | 3 | 2 | 10 | Back, right thigh and leg | None | | Lived |
| 70 | 25 | 3.8 | 0.5 | 9.3 | Both buttocks, both thighs | None | | Died |
| 69 | 21 | 3.7 | 0.3 | 7.2 | Left arm, right forearm, both thighs, left chest wall | None | | Died |
| 78 | 19 | 9 | 22 | 14 | Left thigh, left forearm, right thigh, right leg | Fasciotomy, right leg | 96 | Died |
| 93 | 32 | 8 | 13 | 13.2 | Chest, abdomen, legs, left arm | None | | Died |
| 99 | 23 | <5 | 5 | Nothing I. V. | Left thigh, fracture of right zygoma | Elevation of right zygoma | 120 | Lived |
| 132 | 22 | 1.5 | 4.8 | Immediate therapy | Left shoulder, neck, scalp laceration | Exploration and drainage, neck and shoulder; tracheotomy | 14 | Died 56 hours after release |
| 124 | 23 | 1 | 6 | 8 | All of body except both legs below knee | None | | Lived |

< = less than.

thirty minutes after release that he was evacuated to the rear without treatment. He nevertheless died 4½ days later. Only one patient (Case 93) was in shock when first examined, and this was thirteen hours after release. He had had no previous medical attention. A diagnosis of slight shock was made in one patient (Case 78), twenty hours after release; and though diagnoses of shock were never made in Cases 69 and 132, transitory episodes of impalpable pulse and unmeasurable blood pressure were recorded in the case histories at nineteen hours in Case 69, and at fourteen and twenty-three hours in Case 132. In Case 70, and in all the surviving patients, hypotension was never observed.

*Nausea and vomiting:* Nausea or vomiting was recorded in only three cases, all of which terminated fatally. Nausea with hiccuping was observed in one patient (Case 70). This occurred on the first and second days after release when the nonprotein nitrogen concentration was 83 to 104 mg. per 100 c.c. of plasma. Vomiting was recorded twice. One patient (Case 93) vomited while he was still pinned down by masonry but not afterward. The second patient (Case 78) had troublesome vomiting on the second and third days after release from compression. On those days the nonprotein nitrogen of the plasma was 92 mg. per 100 c.c. and occasionally higher.

*Local changes:* Commonly the appearance of the skin gave no indication of the changes in the underlying muscle. In some patients, however, there were bruises and areas of ecchymosis and lividity of the overlying skin. Immediately after release from compression the affected parts began to swell. The swelling took place first within the fascial compartments and resembled the swelling of the calf muscles following interruption of the popliteal artery. The affected areas became hard, tense, and brawny. Only later, usually after the third day, did soft, pitting subcutaneous edema appear. Distribution of lesions was variable. The extremities were most often involved, particularly the legs, and the muscles of the buttock were frequently included. In one patient (Case 132) the muscles of the shoulder and neck were most affected, and edema of the neck was so great that a tracheotomy proved necessary.

During the first few days of the syndrome the patients might have no complaints or they might complain of stiffness, soreness, aching, and tenderness in the involved areas. Symptoms were often inversely proportional to the severity of injury. In relatively mild lesions, pain was elicited by pressure on the affected area; more severe lesions were insensitive to pressure. Some patients complained of numbness of the skin of the toes and over the involved muscles. Examination revealed patchy areas of hypesthesia or anesthesia of the skin, a "stocking" type of anesthesia of the limbs, and absent reflexes. Involved muscle groups were paralyzed or sometimes temporarily spastic. It was sometimes impossible to feel pulsations in the arteries of the affected limbs, reminding one of the early phase of Volkmann's contracture. In one patient (Case 78) a fasciotomy was done for that reason. The leg was so insensitive that it was possible to perform the operation without further anesthesia.

*Fractures:* Rather surprisingly, in view of the nature of the initial trauma, no major fractures were observed. The only fracture recorded (of the zygoma) could be considered only coincidental.

*Secondary Phase.*—One patient (Case 132) died fifty-six hours after release from compression; the other four lived from four to thirteen days after release. One died suddenly, apparently of acute cardiac failure; the others died more slowly, with progressive lethargy and drowsiness but no typical uremic coma. Drowsiness was particularly marked in one patient (Case 78), who had been treated with magnesium. None of the patients in this group had convulsions at any time during their illness. The mechanism of death in most instances appeared to be pulmonary edema, except in one patient (Case 93), who developed pneumonia on the twelfth day shortly after the appearance of a diuresis had led to hope for his recovery.

All of the patients who died showed the usual signs and symptoms of a lower nephron nephrosis (previously described). The initial urine specimens were deeply pigmented and reacted positively with the benzidine test; oliguria was marked and, except in Cases 69 and 93, progressive (see Table III). The urine, with one exception, was persistently acid, and the specific gravity was constantly low from the third day onward. The nonprotein nitrogen level in the plasma rose progressively, and on the third or fourth day mild hypertension developed. Details of the chemical abnormalities of the blood and urine follow.

TABLE II. DURATION OF ABNORMALITIES IN THE URINE OF NINE PATIENTS WITH CRUSH SYNDROME (DAYS)

| CASE NUMBER | COLOR ABNORMALITY | ALBUMIN | BENZIDINE-POSITIVE SUBSTANCE | | PATIENT'S OUTCOME |
|---|---|---|---|---|---|
| | | | HEMOGLOBIN | MYOGLOBIN | |
| 70 | 3 | 4 | 4 | 1.5 | Died |
| 69 | 2 | 9 | 9 | 1 | Died |
| 78 | 2 | 4 | — | — | Died |
| 132 | 2 | 2 | — | — | Died |
| 93 | 3 | 7* | 4† | 1 | Died |
| 73 | 1 | 1 | — | — | Lived |
| 56 | 1 | 1 | 1 | 0 | Lived |
| 99 | 1 (?) | 0 | 0 | 0 | Lived |
| 124 | 0 | 0 | 0 | 0 | Lived |

0, none.
—, not determined.
*Beyond this time the urine in this patient showed only negligible traces of albumin.
†Beyond this time only traces or faint traces of hemoglobin were recorded.

TABLE III. URINARY OUTPUT IN FIVE FATAL CASES OF CRUSH SYNDROME

| TIME AFTER RELEASE FROM COMPRESSION | URINARY OUTPUT (C.C. PER 24 HOURS) | | | | |
|---|---|---|---|---|---|
| | CASE 69 | CASE 70 | CASE 78 | CASE 93 | CASE 132 |
| Day of release | — | 200 | -- | 150 | — |
| First day after release | 230 | 30 | 350 | 160 | 300 |
| Second day after release | 50 | 85 | 500 | 165 | 30 |
| Third day after release | 45 | 75 | 250 | 130 | — |
| Fourth day after release | 100 | 35 | 160 | 130 | — |
| Fifth day after release | 100 | — | — | 292 | — |
| Sixth day after release | 80 | — | — | 410 | — |
| Seventh day after release | 150 | — | — | 800 | — |
| Eighth day after release | 100 | — | — | 1305 | — |
| Ninth day after release | 450 | — | — | 1935 | — |
| Tenth day after release | — | — | — | 2760 | — |
| Eleventh day after release | — | — | — | 4135 | — |
| Twelfth day after release | — | — | — | 3050 | — |
| Thirteenth day after release | — | — | — | 890 | — |

—, not determined.

PHYSIOLOGICAL AND BIOCHEMICAL FEATURES

*Blood.—*

*Blood volume:* The blood volume was determined immediately upon arrival at the hospital in only two patients with crush injury. The first (Case 93) was the only patient of the group thought to be in severe shock. He had lost one-third of his total blood volume, entirely in the form of plasma, for he showed no evidence of diminution of the total hemoglobin or red cell mass. The hemoconcentration might have been partly responsible for the clinical picture of shock, as severe shock is generally associated with a loss of circulating blood greater than one-third of the normal volume. (See Article I of this series.) The second patient (Case 124) showed no evidence of shock clinically, and no decrease was found in the volume of circulating blood.

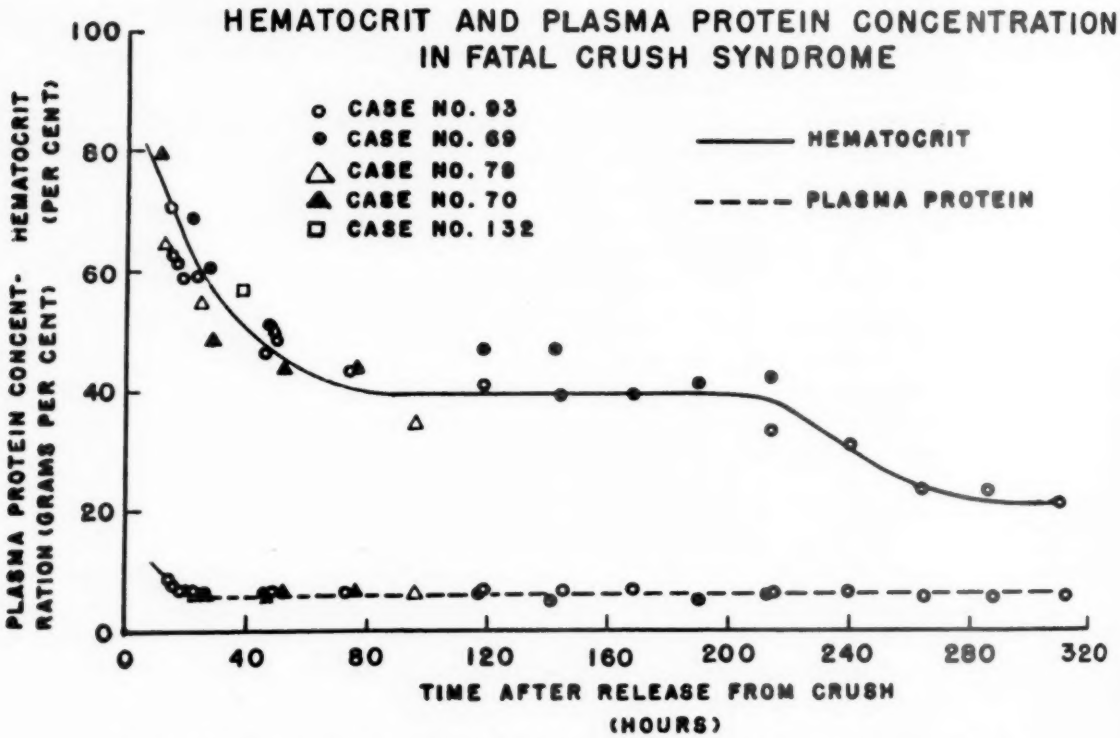


Chart 1.—Hematocrit and plasma protein concentration in fatal crush syndrome.

In three patients (Cases 69, 78, and 93) the blood volume was determined during the course of the disease. It was abnormal in only one of them (Case 78), being increased by about two liters twenty-four hours after release from compression. During that period the patient had received 600 c.c. of plasma (2 "units"), 400 c.c. of 4 per cent sodium bicarbonate, and 1,000 c.c. of 5 per cent dextrose in isotonic saline solution intravenously. He had taken 800 c.c. of liquids by mouth and had voided 350 c.c. of urine. He died three days later with severe pulmonary edema. In Case 93 the patient received no more fluid intravenously than was necessary to correct the blood volume deficit. He died of lobar pneumonia thirteen days after release. The blood and plasma volumes in

Case 69 were within normal limits on the second and ninth days of illness. In retrospect, this patient was given perhaps 2,000 c.c. more parenteral fluid, including large doses of sodium bicarbonate, than optimal. The fact that he developed severe peripheral edema indicates that total body water, if not circulating blood volume, was probably increased.

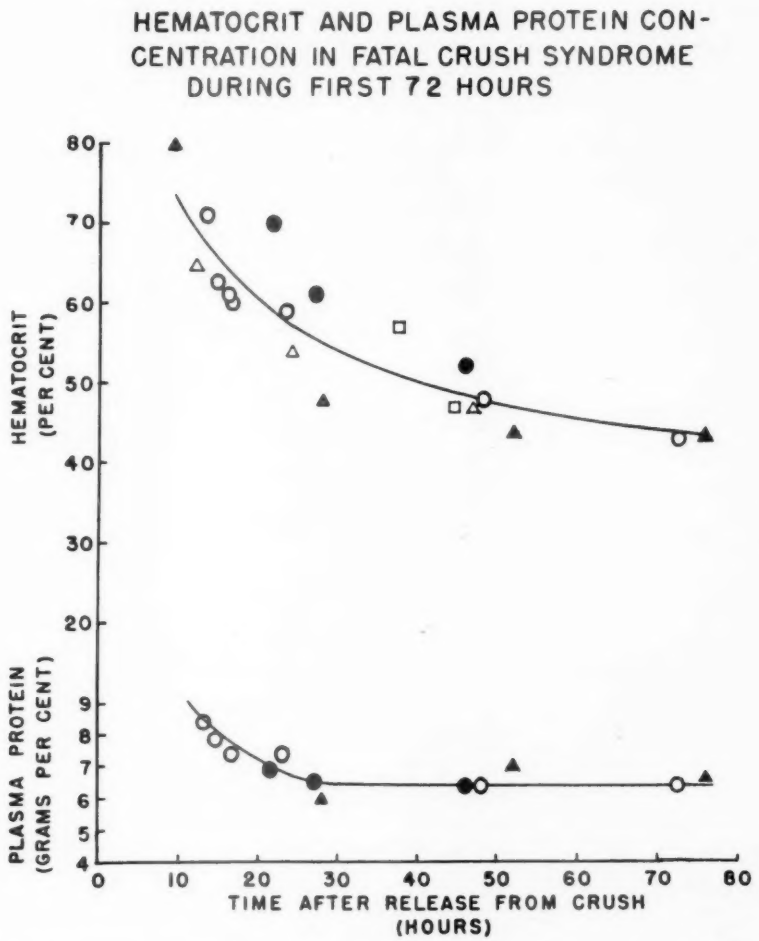


Chart 2.—Hematocrit and plasma protein concentration in fatal crush syndrome during first seventy-two hours.

*Hematocrit value:* The most striking feature of the immediate findings in the blood of patients with the crush syndrome was the hemoconcentration (Chart 1). It was chiefly among these patients with the crush syndrome that hemoconcentration was found in our series of severely wounded. In one patient (Case 70) the estimated hematocrit reading was 80 per cent. It is noteworthy that the clinical evaluation of this case failed to reveal evidence of shock. All of the patients with crush syndrome who died had initial hemoconcentration (Chart 2); all of those who survived showed hematocrit levels within normal limits* on admission (Chart 3). Even in those patients who subsequently died, the

*Normal, 47; range, 42 to 52 per cent.

hemoconcentration was transitory (Charts 1 and 2) and the hematocrit value was within normal limits by the end of fifty hours after release from compression.

*Plasma proteins:* Charts 1 and 2 also indicate a moderate increase in the concentration of plasma proteins* among some patients with crush syndrome; with one exception (Case 56) these increases all occurred in the fatal cases. In general, the concentration of the red blood cells was relatively greater than the concentration of the plasma protein (Chart 4). Again, like the hematocrit values, the plasma protein concentrations had returned to normal before fifty hours had elapsed from the time the patients were released from compression.

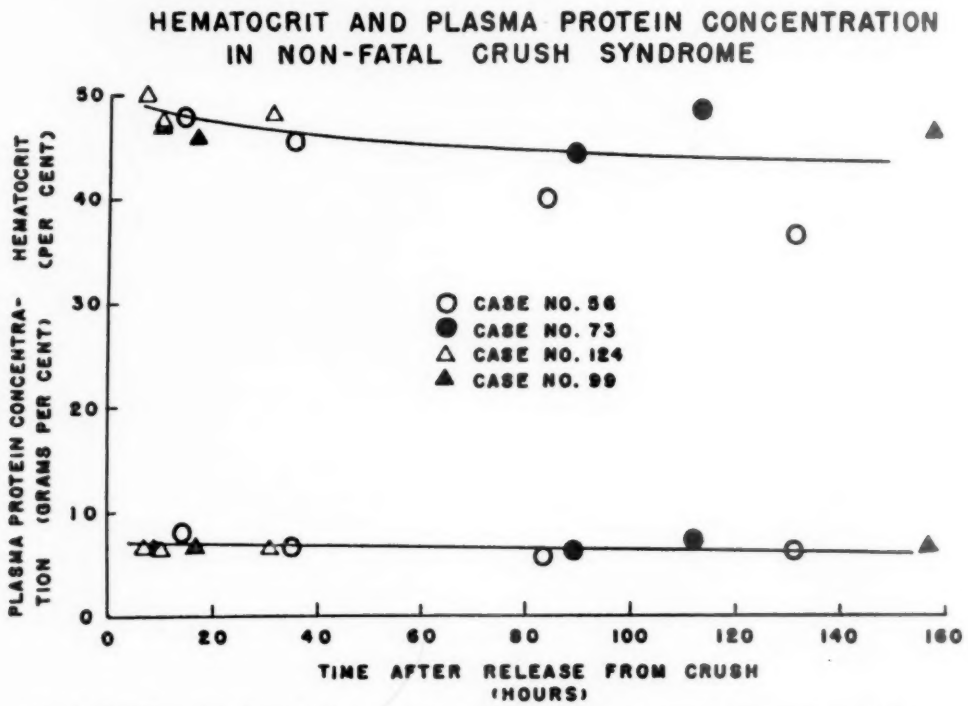


Chart 3.—Hematocrit and plasma protein concentration in nonfatal crush syndrome.

These findings suggest that with release of compression and re-establishment of circulation in the injured areas, there is prompt outpouring of plasma into the compressed parts, manifested clinically by the rapid development of swelling in the affected parts. With the loss of plasma from the circulating blood, the concentration of the red blood cells is increased. If, as is likely, the plasma lost into the tissues contains less protein than normal plasma, an explanation of the early increases in the concentration of plasma proteins in the severe cases is afforded.

The rapid disappearance of the hemoconcentration and of the high plasma protein levels is in part accounted for by the intravenous administration of plasma and crystalloids, but this is not the only factor, for the dilution occurs in the absence of intravenous therapy. The effect could be explained by the reabsorption of extravasated plasma.

*Normal, 6.5; range, 6 to 7 Gm. per 100 c.c.

During the later stages of the illness in the fatal cases, the hematocrit value remained within low normal limits except in Case 93, in which it fell below 40 c.c. cells in 100 c.c. after the sixth day of illness, eventually dropping to 21.9 c.c. cells in 100 c.c. on the day the patient died of lobar pneumonia. There was greater variability in the concentration of the plasma proteins during the course of the disease. The level dropped below 6 Gm. per 100 c.c. (normal, 6.5) in only two patients who survived, but six determinations in patients who died were below 6 Gm. per 100 c.c., three of them being below 5.2 Gm. per 100 c.c. (Charts 1, 2, and 3).

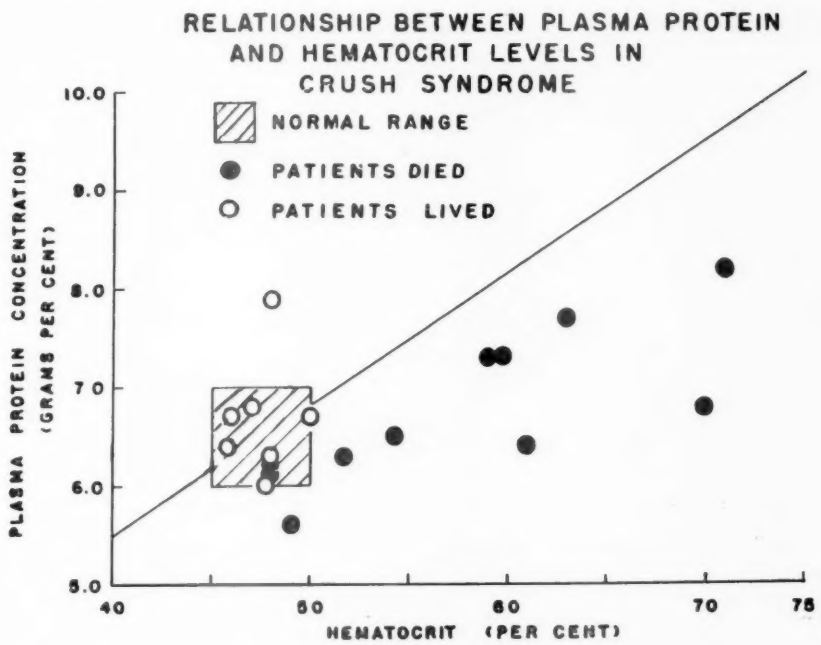


Chart 4.—Relationship between plasma protein and hematocrit levels in crush syndrome. In this chart the diagonal line indicates the locus of a point representing equal dilution or concentration of the red blood cell mass and the plasma protein.

*Plasma nonprotein nitrogen:* Among the patients who survived, the concentration of the nonprotein nitrogen in the plasma was normal throughout the course of the illness. Among those who died, it was elevated from the start and rose progressively at an almost linear rate of approximately 40 mg. every twenty-four hours (Chart 5). The concentration of phosphorus in the plasma rose more slowly and appeared to reach its asymptote earlier.

*Plasma chlorides:* The plasma chloride concentrations were normal among the patients who survived (Chart 6). Among those who developed fatal crush syndrome, however, there was a progressive drop in the concentration of plasma chlorides except in one patient (Case 93) who developed a diuresis and showed evidence of improving renal function, although he subsequently died. At necropsy, lower nephron nephrosis and lobar pneumonia were demonstrated. Concomitant with the fall in plasma chloride level, there was generally a fall in the alkali reserve of the blood, as suggested by the lowering of its carbon dioxide

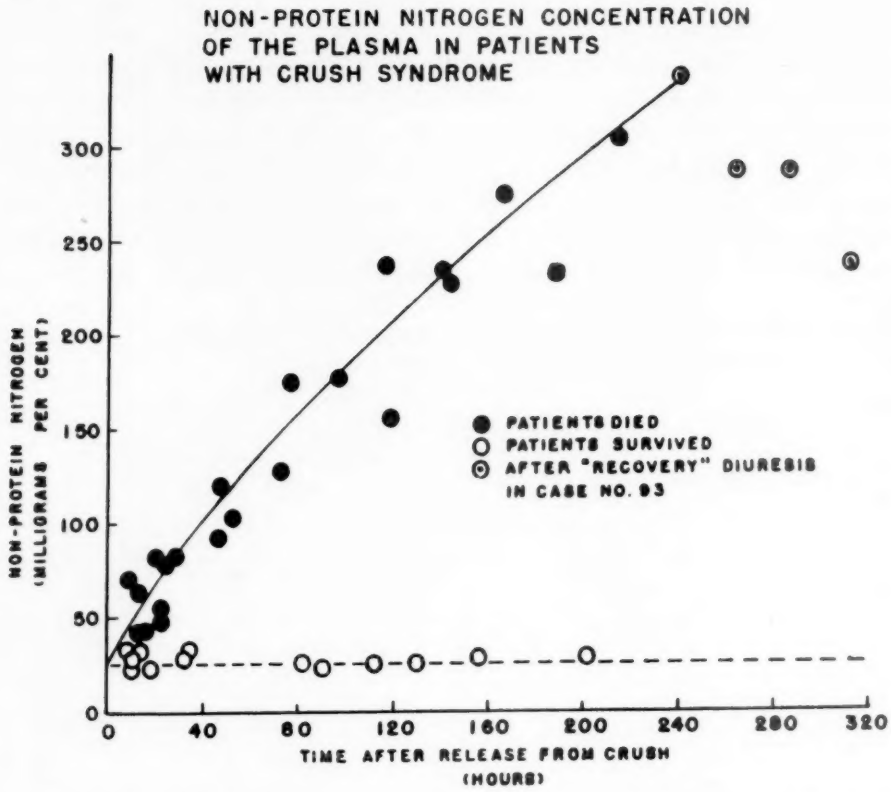


Chart 5.—Nonprotein nitrogen concentration of the plasma in patients with crush syndrome.

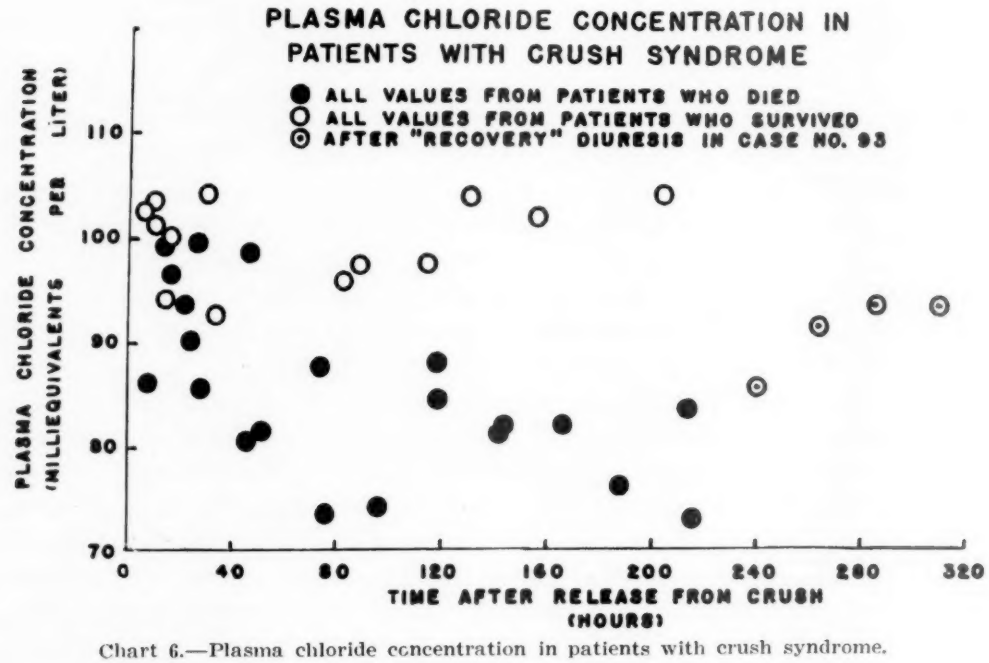


Chart 6.—Plasma chloride concentration in patients with crush syndrome.

combining power. These changes in plasma carbon dioxide combining power and in chloride levels are entirely comparable to those seen in renal insufficiency following other types of trauma. (See preceding papers.)

*Plasma pigment:* Blood specimens taken shortly after release from compression revealed abnormal quantities of a free pigment in the plasma which reacted positively to the benzidine test. Blood samples were collected in carefully dried, but not oiled, syringes and needles. With this technique, a free plasma hemoglobin concentration up to 15 mg. per 100 c.c. was considered within the normal range. Chart 7 illustrates the values obtained both in the patients who died and in those who survived. All but one of the determinations were above the limits accepted as normal; the exception was a determination made in Case 99, nine hours after release from compression. Only one of the

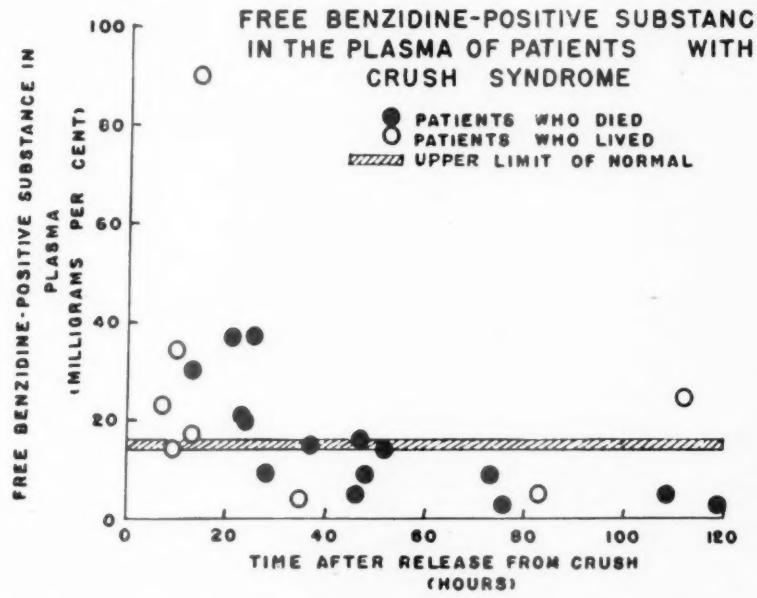


Chart 7.—Free benzidine-positive substance in the plasma of patients with crush syndrome.

patients showed a hemoconcentration of over 40 mg. per cubic centimeter. Of particular interest is the fact that, like the return of the hematocrit level and the plasma protein concentration to normal, the concentration of the free benzidine-positive substance in the plasma was within normal limits by the end of the second day of the disease. As in the case of the hemoconcentration, then, the presence of free benzidine-positive substance in the plasma might be missed if specimens are not collected soon after release from the crushing force.

The nature of this substance, free in the plasma and giving the reaction of a heme, could not be settled. The amounts present were not large enough to make spectroscopic analysis possible in the instrument available to us. Chemical examination of the urine of these patients showed that both hemoglobin and myoglobin were excreted in large amounts, the proportions of each varying widely from case to case. It is reasonable, therefore, to assume that both pigments were represented in the plasma as well.

*Urine.*—Gross abnormalities were found only in the urine specimens collected soon after release from the compression force. Table II indicates the duration of some of the abnormalities in the urine. It will be observed that myoglobin was not found in the urine more than one and one-half days after release from the crushing force, even among the patients who died. Abnormality in the color of the urine lasted somewhat longer (up to three days), and albuminuria, to a significant degree, was detected for as long as nine days after release from the crushing influence.

*Output:* All of the patients who survived the injury had no diminution in the volume of the urinary output below the limits of normal. Of the patients who died (see Table III), all had a diminution in the volume of urine excreted from the start. All had oliguria. In one instance (Case 70) anuria* was recorded during the twenty-four hours beginning the day after release. Two other patients were oliguric until the second twenty-four-hour period, when the output dropped below 100 c.c. a day. Two patients (Cases 78 and 93) were oliguric but never became anuric. One patient (Case 69) had just begun to develop a diuresis when he suddenly died; another (Case 93, Table III) developed an excellent diuresis and might have survived had he not died of lobar pneumonia.

*Color:* Yellow and straw color were considered to be the normal colors of urine. An amber color was considered on the border line of abnormality. All of the patients who died had abnormality of urinary color varying from red to red-brown, or mahogany to dark amber; this lasted two or three days. Among the patients who survived, the color varied from "ruddy" to amber, but this did not persist longer than one day.

*Benzidine-positive pigment:* The grossly abnormal color of the urine in patients with the crush syndrome was found to be caused by the presence of a pigment which reacted positively to the benzidine test. By the technique described in an appendix[8] on Biochemical Methods this pigment was thought to consist of myoglobin as well as hemoglobin in three of the five patients who died of the crush injury. In the fourth patient no attempt was made to differentiate between the two pigments, and in the fifth patient, the benzidine test was not done on the dark amber urine. Results of the tests for myoglobin were never positive in urine specimens obtained later than twenty-four to thirty-six hours after release from the crushing force. Benzidine-positive substance was found later than the second day and up to the eighth day after release, but in such small amounts that it was impossible to employ the test to distinguish between myoglobin and hemoglobin. Qualitative spectroscopic examinations suggested the presence of myoglobin in the specimens obtained in fatal Cases 69, 70, and 93.

*Albumin:* Only two of the patients who survived showed any albuminuria. In neither case did the albuminuria last more than one day, and in only one (Case 56) of the two was it of any degree of severity.

*By our arbitrary definition, anuria was taken to indicate a urinary output of less than 100 c.c. per twenty-four hours.

All of the patients who died showed marked albuminuria. Up to four or six days it persisted unchanged or with increased severity. If the patient lived longer, the degree of albuminuria then decreased, as in Cases 69 and 93. In the latter the urine contained only a faint trace of albumin by the time the patient died of lobar pneumonia, thirteen days after release from the crushing force.

*Sediment:* The urinary sediment was remarkable because findings were so scarce. In one patient who survived (Case 124), no record was made of the examination of the organized sediment. Of the other three patients who lived, only one (Case 73) showed casts in the urinary sediment. On the first day after injury the urine showed occasional coarse and finely granular casts. Two days later the sediment was normal. Two of the five patients who died showed no casts in the urine, although a rare red blood cell and a few white blood cells were found; three did show coarse and finely granular casts in the urinary sediment, but these casts were not abundant even in centrifuged specimens.

*Specific gravity:* For the first day or two of the illness, the specific gravity of the urine was normal in all cases. After the second to fourth days, however, the specific gravity of the urine fell and appeared to become fixed at 1.012 or 1.013. Urine concentration tests were not done in these patients, but as in other cases of posttraumatic renal insufficiency, early impairment of ability to reabsorb water by the renal tubules is surely a characteristic feature.

*Reaction:* With one exception, the patients passed acid urine at all times throughout the illness. This one exception (Case 69) was a patient whose urine was on the alkaline side of neutral (pH 7.2) on two occasions on the seventh and eighth days of the illness. At all other times the urine in this patient was acid, despite administration of sodium bicarbonate in doses thought adequate for alkalinization of the urine (16 to 36 Gm. per twenty-four hours). As had been found in the study of patients who had renal insufficiency from other causes, alkalinization of the urine by means of the administration of sodium bicarbonate was inconsistent with safety.

*Liver Function.*—The function of the liver was tested in one of the four patients who survived and in four of the five patients who died. The examination consisted of a test of the ability of the liver to excrete bromsulfalein injected intravenously. The dosage was calculated on the basis of 5 mg. of bromsulfalein per kilogram of body weight (see Article I). By this method, retention of the dye up to 3 per cent of the dose after forty-five minutes was considered the upper limit of normal.

In the patient who survived, the function of the liver was found to be normal as tested by this method. In all of the patients who died, the liver function was found to be impaired. In all of them, the retention was over 7.2 per cent (Chart 8). The average of ten determinations in the four fatal cases was 12 per cent. This excludes one determination done in Case 93 which showed 26 per cent retention on the day the patient died of lobar pneumonia. One value in each of two cases is recorded as approximate on the chart. These

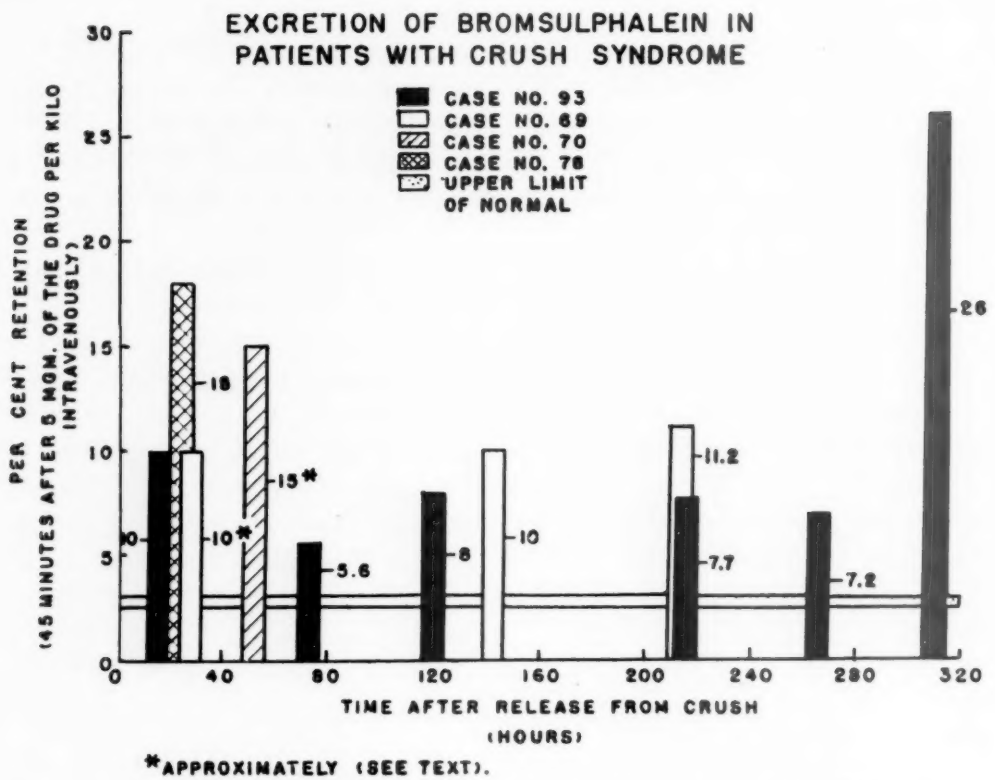


Chart 8.—Excretion of bromsulfalein in patients with crush syndrome. One value in each of two cases is recorded as approximate on the chart. These values were estimated for a forty-five minute period as the figures had been recorded at thirty and sixty minutes in those two instances. The approximate figures are probably within the limits of error of the method.

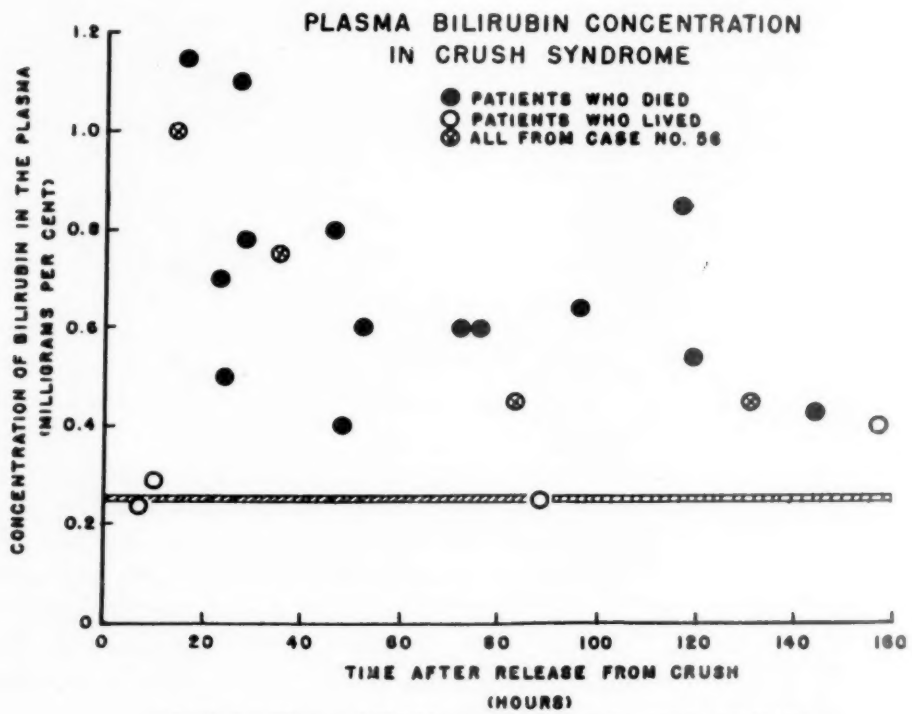


Chart 9.—Plasma bilirubin concentration in crush syndrome.

values were estimated for a forty-five minute period, as the figures had been recorded at thirty and sixty minutes in those two instances. The approximate figures are probably within the limits of error of the method.

Chart 9 indicates the increased concentration of bilirubin in the plasma of patients who developed fatal crush syndrome and in one patient (Case 56) who survived. Sufficient information was not available to distinguish between increased production of bilirubin and decrease in its elimination.

### PATHOLOGY

The important findings at post-mortem examination were confined to the lungs, the liver, the skeletal muscles, and the kidneys.

*Lungs.*—All of the five fatal cases showed slight to extensive pulmonary edema, both grossly and microscopically. The weight of the two lungs together was recorded in four of the five fatal cases. The weights varied from 1,075 to 1,600 grams. Blood as well as edema fluid appeared on cut surfaces of the lungs in Case 132 and microscopically, large numbers of alveoli were packed with red blood cells. This patient had had a tracheotomy, and the blood may have been aspirated. Another patient (Case 78) was unusual in that even the visceral pleura was edematous. Fluid poured from the cut surfaces without outside compression, and the tracheobronchial tree was filled with nonbloody fluid. In Case 93 death was due primarily to lobar pneumonia involving the left upper lobe. Microscopically, in addition to the typical pneumonic process, some areas showed edema with spreading pneumonic involvement.

*Liver.*—In view of the decreased liver function, as measured by ability to excrete bromsulfalein (see Chart 8) and as indicated by the elevated plasma bilirubin (see Chart 9) and the abnormally low ratio of urea-nitrogen to total nonprotein nitrogen, some histologic changes were expected in the liver. Surprisingly few were found. The liver was microscopically normal in Case 70, and showed only scattered vacuoles in Case 132. In Case 69 occasional mitotic figures were observed in hepatic cells, and in Case 93, which showed terminally a rising bilirubin concentration in the blood and a terminal bromsulfalein retention of 26 per cent, the only histologic changes found were mild nuclear atypicality in the cells at the centers of the lobules.

*Skeletal Muscles.*—The gross changes in the involved muscles were conspicuous. In the involved areas the normal pigment had disappeared, leaving muscle bundles with the appearance of fish or rabbit flesh. Sometimes an entire muscle was decolorized, more commonly only segmental areas, particularly regions close to major bony structures. Complete depigmentation of the distal half of the forearm muscles is sometimes apparent, whereas the proximal half is normally colored. The transition from normally colored to depigmented areas was sharp, particularly in the cases of longer survival, and in Case 93 (thirteen days) the junction was marked by a narrow white band 2 to 3 mm. broad. In spite of the loss of color the tissue remained moist, capillary oozing appeared from cut surfaces, and no thrombi could be discovered in any grossly visible vessels. Hemorrhage and edema were extremely irregular in extent and in-

tensity, absent from some lesions and marked in others. The gross depigmentation correlated with chemical assays showing almost complete loss of myoglobin in the affected areas (Table IV).

TABLE IV. MYOGLOBIN CONTENT OF MUSCLE AND KIDNEY IN FOUR PATIENTS WHO DIED FROM CRUSH SYNDROME

| TISSUE | MYOGLOBIN CONTENT (GRAMS PER KILOGRAM OF WET TISSUE) | | | |
|---|---|---|---|---|
| | CASE 69 | CASE 70 | CASE 78 | CASE 93 |
| Normal muscle | 2.1* | 3.6 | 4.2 | 3.74 |
| Depigmented muscle | 1.0 | 0.27 | 0.83 | 0.54 |
| Partly depigmented muscle | 1.86 | — | 3.0 | — |
| Kidney | 0.45 | 0.6 | 0.93 | — |

*This low value is probably due to the extensive interstitial edema in this patient.

Microscopic sections were available from four cases, four, five, ten, and thirteen days, respectively, after injury. In the acute cases hematoxylin and eosin stains showed relatively inconspicuous changes. Evidence of muscle-cell degeneration, however, were present. Some cells were swollen, hyaline, and more strongly acidophilic than normal. More commonly the cells stained less intensely than normal, cross striations were exaggerated, occasional fractures and clefts were present, and the sarcolemma nuclei appeared decreased in number. Though edema and hemorrhage were apparent in some areas, there was no inflammatory reaction, either polymorphonuclear or histiocytic. With the Masson and phosphotungstic acid hematoxylin stains, the changes were far more conspicuous. Some of the swollen hyaline fibers stained intensely red with the Masson, or blue with the phosphotungstic stain, but the great majority responded feebly or not at all to the specific staining reactions. In sections across the border of a depigmented area it was evident that the loss of specific staining reaction corresponded closely with the margin of depigmentation. It was of interest that the cells with exaggerated cross-striations usually failed to stain specifically.

In the cases of longer duration (ten and thirteen days), changes were conspicuous with all staining methods but particularly with hematoxylin and eosin. Many swollen, necrotic muscle cells had become intensely basophilic owing to the precipitate of innumerable fine granules staining like calcium throughout the sarcoplasm. In other cells the precipitate was intense in the central portion but absent at the periphery. Another common type of degenerative change was a coarse hydropic vacuolation which frequently produced an appearance suggestive of vegetable cells. Other degenerating cells showed varying degrees of infiltration with histiocytes. The sarcolemma nuclei in many cells showed amitotic division with chains of touching nuclei 5 to 10 elements in length. About many of these, viable cytoplasm was present in long, slender masses suggesting regeneration of muscle cells. The interstitial connective tissue was slightly edematous and densely infiltrated with histiocytes. No definite evidence of fibroblastic proliferation could be made out. Blood vessels still remained free from thrombi or inflammatory reaction.

*Kidneys.*—In all but one patient (Case 70) the kidneys were enlarged at necropsy. In three of the five fatal cases the combined weights of the two kidneys were recorded and were respectively 500, 550, and 625 grams. The capsules stripped easily. In some there were ecchymoses beneath the capsule. Focal hemorrhages and fibrin deposits were commonly found beneath and on the epithelium of the renal pelvis. When the kidneys were cut, with one exception (Case 70) the renal parenchyma pouted through the cut, rolling outward and forming a rounded instead of a sharp edge.

Characteristically, the cut surface of the parenchyma showed pallor of the cortex and darkening of the pyramids to a dark brown or mahogany color. The thickness of the cortex was normal or increased, never decreased.

The microscopic appearances of the kidneys in patients who died with crush syndrome have been described and illustrated elsewhere (in our paper on "The Pathology of the Kidney in Traumatic Shock" as a "lower nephron nephrosis") and it will be sufficient merely to list the salient features here.

*Microscopic Kidney.*—Most conspicuous was the presence of densely pigmented casts in the distal convoluted and the collecting tubules. These could not be distinguished in stained or unstained sections from the pigmented casts in Case 9, a known transfusion reaction. Proximal to the pigmented casts, usually in the ascending limbs of Henle's loops, hyaline nonpigmented casts were numerous. In cases with survival periods of four days, these hyaline casts were frequently extruded into the stroma and formed foci for granulomatous reactions. Degenerative changes in the renal parenchyma were limited to the lower nephron segments, usually the ascending limbs, less often the distal convoluted tubules.

Glomeruli were uniformly normal except for the presence of granular precipitate in the capsular space. The proximal convoluted tubules were sometimes moderately dilated and their lumina contained granular precipitate, but the epithelial cells were normal and brush borders were well preserved. Interstitial inflammatory reaction was always present at the corticomedullary junction, and in two cases, of ten and thirteen days' duration, a narrower zone of interstitial inflammatory reaction was seen beneath the capsule. In the same two cases nonocclusive thrombi were present in some of the veins at the corticomedullary junction.

## TREATMENT OF CRUSH SYNDROME

The results of treatment in patients who developed the crush syndrome were disappointing. (Our ministrations were certainly less effective than those of Saint Benedict, whose successful treatment of a monk crushed beneath the masonry of a wall at Monte Cassino is the subject of a fourteenth century Florentine fresco.) In general, efforts during the first forty-eight hours were directed toward correction of the hemoconcentration and attempts at alkalinization of the urine. Subsequently, the treatment was that for renal insufficiency as described for patients with renal insufficiency from other causes.

*Correction of Hemoconcentration.*—Hemoconcentration was treated by administration of plasma and crystalloid solutions during the first forty-eight hours. Beyond this time, the degree of hemoconcentration was no longer a

serious problem, for reabsorption had probably begun to exceed transudation. Only two of the nine patients received whole blood. One of the two (Case 69) received only 250 c.c. of blood, administered before the hemoconcentration had been recognized. The other (Case 132) was given 1,500 c.c. of whole blood when he became pulseless and no blood pressure could be determined in the extremities.

*Alkalinization of the Urine.*—According to Bywaters' hypothesis, alkalinization should be started at the time the casualty is found, immediately after or even before release from compression. This was not possible in any of our patients. The seriousness of the injury was not recognized by the aid-men. As a matter of fact, the diagnosis was not made by the medical officers until, through an educational campaign, they had been made aware of the possibility of the syndrome in any crush injury.

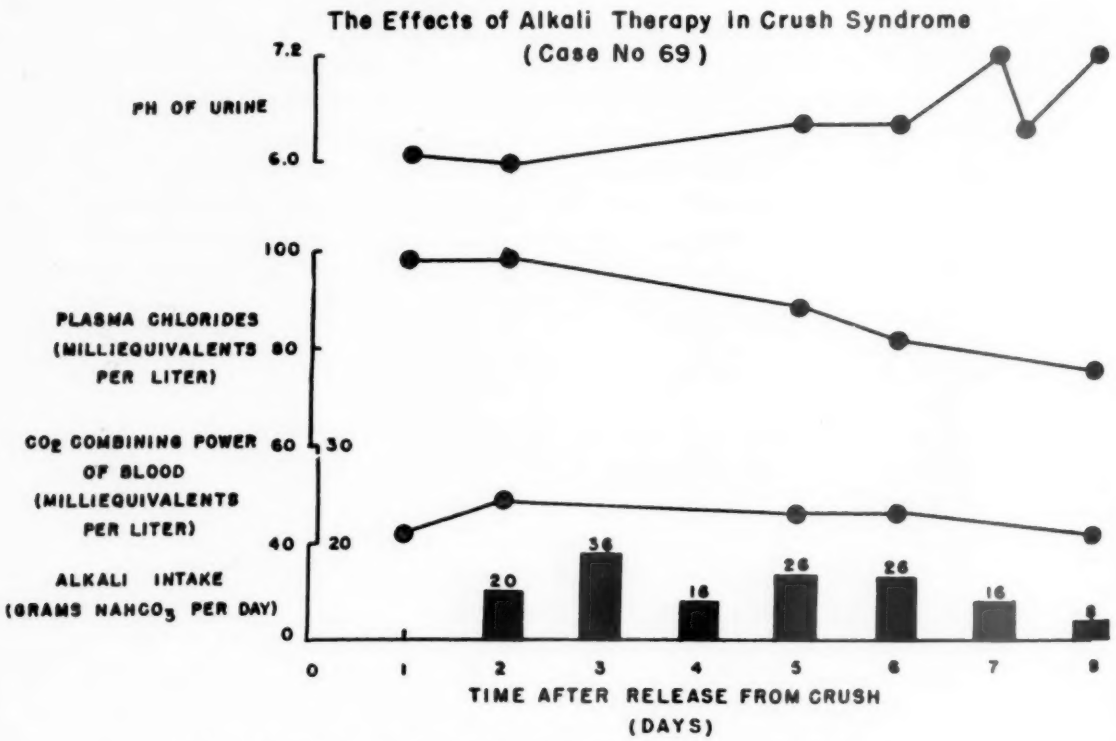


Chart 10.—The effects of alkali therapy in crush syndrome (Case 69).

After admission to the hospital, however, all but two of the nine patients received alkali therapy. Four of the five patients who died were treated with alkali; one was started promptly upon admission to the hospital, one during the first twenty-four hour period after release from the crushing force, and two during the second twenty-four hour period. No beneficial effects were observed that could be attributed to the alkali. The most striking feature was the failure, in the fatal cases, to succeed in alkalinizing the urine. A pH of 7.2 was attained in only two specimens of urine in Case 69 (Chart 10). This patient had received larger doses of sodium bicarbonate than the other patients. One patient in this group (Case 124) did develop an alkaline urine (pH 8.4)

within four hours after intravenous administration of sodium bicarbonate, and it was kept alkaline by the administration of 3 Gm. of the bicarbonate every four hours. This patient had a minimal renal lesion and survived. Administration of sodium bicarbonate was done cautiously or abandoned altogether, because of unfortunate experiences with vigorous attempts at alkalinization in patients with renal insufficiency from other causes.

*Diuretics.*—Alcohol was used with the hope that it would promote blood flow through the kidney and serve as a diuretic. It was used intravenously (total dose 50 to 100 c.c. of 95 per cent ethyl alcohol) as a 5 per cent solution in dextrose or isotonic saline solution, and as whiskey by mouth (60 to 180 c.c. per day). No beneficial effects were detected that could be attributed directly to the alcohol. Three of the patients were given 10 per cent dextrose in distilled water intravenously and one was given 50 per cent dextrose intravenously as a diuretic, but no effect was noted in any of them that could be attributed to the medication. The failure of both alcohol and hypertonic solutions of dextrose to promote urine flow or improve kidney function confirmed the findings in patients with renal insufficiency from other causes.

Not only did concentrated solutions fail to induce a diuresis, but in three cases (Cases 70, 78, and 132) the hypertonic dextrose solution may have hastened the onset of pulmonary edema. Mercurial diuretics were not tried in patients with the crush syndrome.

*Dehydrating Agents.*—On the hypothesis that swelling and edema of the kidney may be in part responsible for failure of function, the use of potassium and magnesium solutions was recommended by Barker[9] to reduce the tissue swelling and to promote diuresis. Potassium chloride was not available to us for clinical use, but magnesium sulfate was used intravenously and intramuscularly. It was employed in three cases (Cases 69, 78, and 93) in dosage of 4 to 8 Gm. daily for three to five days, which was sufficient to elevate the concentration of magnesium in the blood as indicated in the two patients in whom such analyses were made (Cases 78 and 93). In these three patients there was no definite effect upon urinary output, and it is impossible to attribute any beneficial effect to the use of magnesium. Unusual drowsiness in one patient (Case 78) could well have been caused by the magnesium therapy, for his serum concentration of magnesium was 5.8 meq. per liter at necropsy. The serum magnesium reached a level of 6.8 meq. per liter at one stage during the course of treatment in Case 93. For the same reasons stated earlier, it is our opinion that neither magnesium nor potassium solutions should be used in the treatment of this syndrome.

*Other Measures.*—Study of these nine patients taught us little as to possible means of preventing anuria or inducing diuresis. Generally accepted methods failed. On the hypothesis that the injury to the kidney may be produced when reabsorption of extravasated fluid takes place, pressure bandages were considered worthy of trial and were applied in one patient (Case 78) without apparent effect. In this case, however, serious extravasation into the tissues had already occurred before the patient reached the hospital. Cold applications might prevent rapid flooding of the kidney with large

quantities of muscle-breakdown products, inasmuch as cold is known to inhibit the flow of lymph from the periphery into the general circulation. This therapy was not tried. Again, however, to be effective, it would have to be started immediately after release from compression. Therapeutic amputation of the involved extremities was thought to be out of the question for the same reason.

It was learned from the patients with crush syndrome, as well as from those with renal insufficiency from other causes, that it is very easy to bring about an increase in plasma volume in these patients by vigorous attempts at inducing a diuresis with intravenous crystalloids. Once oliguria or anuria is established, it is best to withhold fluid, allowing just enough fluid, preferably by mouth, to compensate for loss from the gastrointestinal tract, for insensible loss through the skin, from the lungs, and from the sweat glands. Under ordinary circumstances, these requirements can be met by 1,000 c.c. or less of fluid daily; more must be allowed if excessive extrarenal losses occur. In general, patients with renal insufficiency have been found to be over- rather than underhydrated, and this accounts for the fact that pulmonary edema is a common cause of death.

## SUMMARY

A laboratory and clinical study was made of nine patients who received crushing injuries; four of the patients survived, and five died. It is emphasized that the syndrome develops insidiously in patients who appear well when first seen. All patients who have suffered compression interfering with the circulation in muscle masses for periods of one hour, or perhaps even less should be observed carefully for development of features of the syndrome: namely, tense swelling of the affected parts, hemoconcentration, benzidine-positive pigment (presumably myoglobin) free in the plasma and urine, and oliguria or anuria. If examinations are not made within twenty-four or forty-eight hours, the hemoconcentration and the myoglobinuria will be missed. The volume of urinary output should be watched closely, for significant oliguria may easily be overlooked.

The principal pathologic findings are in the compressed muscles and in the kidneys. In the former the normal pigment, myoglobin, is rapidly mobilized and absorbed, and extensive necrosis of muscle develops which tends to heal with calcification if the patient survives one week or longer. In the kidney a pigment nephropathy is found, which is indistinguishable from that which develops following other forms of severe trauma. A common terminal finding is severe pulmonary edema.

The treatment applied to these nine cases has been described. In the presence of oliguria and anuria, it has been impossible to alkalinize the urine with the doses of sodium bicarbonate which could be administered without the danger of producing severe metabolic alkalosis. It is particularly important not to flood the circulatory system with intravenous solutions in an attempt to induce diuresis, once oliguria or anuria has become established.

## CONCLUSIONS

1. The crush syndrome is a clinical entity which bears a high case-fatality rate and should be suspected in any patient who suffers a compressing injury.

2. The syndrome develops insidiously in patients who may appear well when first seen.

3. Immediate alkalinization, as recommended by Bywaters, is difficult to apply in practice, particularly under conditions of combat, because the patient has usually been extricated some time before the medical officer sees him and the damage to the kidney has probably already been done.

4. Alkalinization, once oliguria or anuria has become established, is both difficult and dangerous.

5. Of first importance in the management of the crush syndrome in the anuric or oliguric phase is to avoid excessive parenteral fluid administration (in vigorous efforts to induce diuresis). When excessive fluid is administered, the patient may die of pulmonary edema before fatal uremia develops.

6. A recovery diuresis may develop in these cases. This is shown by two patients in this series in whom recovery diuresis had begun before death; in one of them it was well developed.

The cases of special interest in this paper are: fatal, cases 69, 70, 78, 93, 132; nonfatal, cases 56, 73, 99, and 124.

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# Book Reviews

**Operating Room Technique.** By Edythe Louise Alexander, R.N., Supervisor of Operating Rooms of the Roosevelt Hospital, New York, N. Y. Ed. 2. pp. 765 with 668 illustrations. St. Louis, The C. V. Mosby Company, 1949.

The scope of this comprehensive textbook of operating room nursing techniques is amazing. One-third of the book is devoted to discussion of general principles and techniques; the remainder to techniques for individual operative procedures. Throughout, there is a pleasing combination of the scholarly presentation of such features as the anatomy and physiology of the operative region under consideration plus detailed and realistic outlines of technical nursing procedures.

In the presentation of operative procedures, the operative and corresponding nursing techniques are conveniently placed in parallel columns. The text is well illustrated, particularly in the demonstration of general procedures such as sterilization, instrument arrangement, and the draping of the operative field.

The book is apparently primarily designed to aid supervisors in the teaching of nurses and as a convenient reference text for the student herself. Considering the many related subjects presented it is remarkable that a single author has such an adequate grasp of the material. The volume is recommended as a comprehensive, readable, yet practical text of nursing techniques in the operating room.

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**Descriptive Atlas of Radiographs.** By A. P. Bertwistle, M.B., Ch.B., F.R.C.S. (Ed.); 7th Edition. 622 pp., with 980 illustrations. St. Louis, 1949, The C. V. Mosby Company.

This is not a textbook of roentgenographic diagnosis but is, as Dr. Bertwistle points out, an atlas of radiographs primarily intended for the use of the clinician who desires to know what roentgenograms are capable of revealing to him and thus encourage him to resort to radiology when confronted with clinical difficulties. Illustrative radiographs cover the subjects of normal bones and epiphyses, congenital abnormalities, fractures, diseases and tumors of bone, injuries and diseases of joints, nasal system, dental system, alimentary system, urinary system, respiratory system, nervous system, vascular system, ductless glands, female generative system, and muscles. Radiographs are also included on medico-legal cases, embryology, anthropology, helminthology, and occupational diseases. Each figure is discussed from the standpoint of the radiographic evidence and, in many cases, a short clinical history and general discussion are included. The radiographs are representative and in some instances a line drawing is included with the illustration to increase the clarity.